VOLUME VIII OF VIII
MOTTOLO SITE
REMEDIAL INVESTIGATION REPORT
APPENDIX C-8

Submitted to:

United States Environmental Protection Agency
Region I
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Boston, Massachusetts 02203

Prepared on behalf of:

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September 28, 1990
Balsam Project 6185/818

(S4324COV)

APPENDIX C-8

TECHNICAL SUMMARIES FOR INDICATOR COMPOUNDS

C-8 (a) ARSENIC

C-8 (a)

ARSENIC

The attached Information Risk Information System (IRIS) printout (March 1990) is provided as a technical summary for arsenic. As discussed in the does-response section, although a large data base exists regarding arsenic toxicity, many variables affect the actual toxicity of arsenic. In particular, the form that the arsenic takes (organic versus inorganic, and trivalent versus pentavalent) will make a significant difference in the resultant toxicity. Furthermore, some studies have shown that, at low levels, arsenic may be an essential nutrient. Because of this uncertainty related to arsenic toxicity, the National Primary Drinking Water Regulation (NPDWR) and New Hampshire Division of Public Health Services (NHDPHS) health criteria for arsenic of 50 ug/l was considered as the action level for arsenic in site ground water. However, the resultant risks estimated from ingestion of ground water with this concentration of arsenic were not within the acceptable range of 1E-04 to 1E-06. Furthermore, the levels of arsenic observed in some of the off-site wells and on-site wells not affected by on-site disposal activities, would also result in the prediction of risks greater than the 1E-04 to 1E-06 range. For these reasons, and because the average on-site ground water arsenic concentrations was similar in value to some concentrations observed in unaffected wells, the arsenic NHDPHS health criteria and NPDWR of 50 ug/l was selected as the more appropriate basis to assess risks associated with this exposure scenario. Thus, because both the average and maximum plausible arsenic exposure point concentration of 28 ug/l and 36 ug/l, respectively, for Area 1 bedrock are less than the arsenic NHDPHS health criteria and NPDWR of 50 ug/l, significant site risks associated with possible future use of this site ground water as a domestic water supply source and attributable to arsenic were not identified.

Arsenic, inorganic; CASRN 7440-38-2 (10/01/89)

Health risk assessment information on a chemical is included in IRIS only after a comprehensive review of chronic toxicity data by work groups composed of U.S. EPA scientists from several Program Offices. The summaries presented in Sections I and II represent a consensus reached in the review process. The other sections contain U.S. EPA information which is specific to a particular EPA program and has been subject to review procedures prescribed by that Program Office. The regulatory actions in Section IV may not be based on the most current risk assessment, or may be based on a current, but unreviewed, risk assessment, and may take into account factors other than health effects (e.g., treatment technology). When considering the use of regulatory action data for a particular situation, note the date of the regulatory action, the date of the most recent risk assessment relating to that action, and whether technological factors were considered. Background information and explanations of the methods used to derive the values given in IRIS are provided in the five Background Documents in Service Code 5, which correspond to Sections I through V of the chemical files.

STATUS OF DATA FOR Arsenic, inorganic

File On-Line 02/10/88

Category (section)	Status	Last Revised
Oral RfD Assessment (I.A.)	pending	
Inhalation RfD Assessment (I.B.)	no data	
Carcinogenicity Assessment (II.)	on-line	09/01/89
Drinking Water Health Advisories (III.A.)	no data	
U.S. EPA Regulatory Actions (IV.)	on-line	03/01/88

I. CHRONIC HEALTH HAZARD ASSESSMENT FOR NONCARCINOGENIC EFFECTS

Substance Name -- Arsenic, inorganic
CASRN -- 7440-38-2

A risk assessment for this chemical will be reviewed by an EPA work group.

II. CARCINOGENICITY ASSESSMENT FOR LIFETIME EXPOSURE

Substance Name -- Arsenic, inorganic
CASRN -- 7440-38-2
Last Revised -- 09/01/89

Section II provides information on three aspects of the carcinogenic risk assessment for the agent in question; the U.S. EPA classification, and quantitative estimates of risk from oral exposure and from inhalation exposure. The classification reflects a weight-of-evidence judgment of the likelihood that the agent is a human carcinogen. The quantitative risk estimates are presented in three ways. The slope factor is the result of application of a low-dose extrapolation procedure and is presented as the risk per mg/kg/day. The unit risk is the quantitative estimate in terms of either risk per ug/L drinking water or risk per ug/cu.m air breathed. The third form in which risk is presented is a drinking water or air concentration providing cancer risks of 1 in 10,000, 1 in 100,000 or 1 in 1,000,000. Background Document 2 (Service Code 5) provides details on the rationale and methods used to derive the carcinogenicity values found in IRIS. Users are referred to Section I or information on long-term toxic effects other than carcinogenicity.

<<< Arsenic, inorganic >>>

II.A. EVIDENCE FOR CLASSIFICATION AS TO HUMAN CARCINOGENICITY

II.A.1. WEIGHT-OF-EVIDENCE CLASSIFICATION

Classification -- A; human carcinogen

Basis -- based on observation of increased lung cancer mortality in populations exposed primarily through inhalation and on increased skin cancer incidence in several populations consuming drinking water with high arsenic concentrations.

<<< Arsenic, inorganic >>>

II.A.2. HUMAN CARCINOGENICITY DATA

Studies of smelter worker populations (Tacoma, WA; Magma, UT; Anaconda, MT; Ronnskar, Sweden; Saganoseki-Machii, Japan) have all found an association between occupational arsenic exposure and lung cancer mortality (Enterline and Marsh, 1982; Lee-Feldstein, 1983; Axelson et al., 1978; Tokudome and Kuratsune, 1976; Rencher et al., 1977). Both proportionate mortality and cohort studies of pesticide manufacturing workers have shown an excess of lung cancer deaths among exposed persons (Ott et al., 1974; Mabuchi et al., 1979). One study of a population residing near a pesticide manufacturing plant revealed that these residents were also at an excess risk of lung cancer (Matanoski et al., 1981). Case reports of arsenical pesticide applicators have also demonstrated an association between arsenic exposure and lung cancer (Roth, 1958).

A cross-sectional study of 40,000 Taiwanese exposed to arsenic in drinking water found significant excess skin cancer prevalence by comparison to 7500 residents of Taiwan and Matsu who consumed relatively arsenic-free water (Tseng, 1977). This study design limited its usefulness in risk estimation. Arsenic-induced skin cancer has also been attributed to water supplies in Chile, Argentina and Mexico (Borgono and Greiber, 1972; Bergoglio, 1964; Cebrian et al., 1983). No excess skin cancer incidence as been observed in U.S. residents consuming relatively high levels of arsenic in drinking water (Morton et al., 1976; Southwick et al., 1981). These U.S. studies, however, are not inconsistent with the existing findings from the foreign populations. The statistical powers of the U.S. studies are considered to be inadequate because of the small sample size.

A study of the population living in the same area of Taiwan studied by Tseng (1977), where arsenic contamination of the water supply was endemic, found significantly elevated standard mortality ratios for cancer of the bladder, lung, liver, kidney, skin and colon. A case control study of bladder, liver and lung cancer cases in the endemic area found a significant association with arsenic exposure that was dose-related. The association of arsenic ingestion and cancer of various internal organs has also been cited in a number of case reports. Persons treated with arsenic-containing medicinals have also been shown to be at a risk of skin cancer (Sommers and McManus, 1953).

II.A.3. ANIMAL CARCINOGENICITY DATA

None. There has not been consistent demonstration of arsenic carcinogenicity in test animals for various chemical forms administered by different routes to several species (IARC, 1980). There are some data to indicate that arsenic may produce animal tumors if retention time in the lung can be increased (Pershagen et al., 1982, 1984).

II.A.4. SUPPORTING DATA FOR CARCINOGENICITY

Sodium arsenic has been shown to transform Syrian hamster embryo cells (Dipaolo and Casto, 1979) and to produce sister-chromatid-exchange in DON cells, CHO cells and human peripheral lymphocytes exposed in vitro (Wan et al., 1982; Ohno et al., 1982; Larramendy et al., 1981; Andersen, 1983; Crossen, 1983). While arsenic compounds have not been shown to mutate bacterial strains, it produces preferential killing of repair deficient strains (Rossman, 1981).

II.B. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM ORAL EXPOSURE

The Risk Assessment Forum has completed a reassessment of the carcinogenicity risk associated with ingestion of inorganic arsenic. This report, which has been extensively peer-reviewed by outside reviewers (including SAB review) concluded that the most appropriate basis for an oral quantitative estimate was the study by Tseng et al. (1977), which reported increased prevalence of skin cancers in humans as a consequence of arsenic exposure in drinking water. Based on this study a unit risk of 5E-5/ug/L as proposed.

A recent memorandum by the Administrator of the EPA recommended that the above slope factor be adopted. The memorandum further counsels that "in reaching risk management decisions in a specific situation, risk managers *must recognize and consider the qualities and uncertainties of risk* estimates. The uncertainties associated with ingested inorganic arsenic are such that estimates could be modified downwards as much as an order of *magnitude, relative to risk estimates associated with most other* carcinogens. In such instances, the management document must clearly articulate this fact and tate the factors that influenced such a decision."

------<<< Arsenic, inorganic >>>------

II.C. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM INHALATION EXPOSURE

II.C.1. SUMMARY OF RISK ESTIMATES

Inhalation Slope Factor -- 5.0E+1/mg/kg/day

Inhalation Unit Risk -- 4.3E-3/ug/cu.m

Extrapolation Method -- absolute-risk linear model

Air Concentrations at Specified Risk Levels:

Risk Level	Concentration
E-4 (1 in 10,000)	2E-2 ug/cu.m
E-5 (1 in 100,000)	2E-3 ug/cu.m
E-6 (1 in 1,000,000)	2E-4 ug/cu.m

II.C.2. DOSE-RESPONSE DATA FOR CARCINOGENICITY, INHALATION EXPOSURE

Species/Strain	Dose	Tumor

Reference

Tumor Type	Administered	Human Equivalent	Incidence

------<<< Arsenic, inorganic >>>------

Human, male lung cancer — Route: Inhalation; occupational exposure

Ambient Unit Risk Estimates

Exposure Source	Study	Unit Risk	Geometric Mean Unit Risk	Final Estimates Unit Risk
Anaconda smelter	Brown and Chu, 1983a,b,c	1.25 E-3		
	Lee-Feldstein, 1983	2.80 E-3	2.56 E-3	
	Higgins, 1982; Higgins et al., 1982; Welch et al., 1982	4.90 E-3		4.29 E-3
ASARCO smelter	Enterline and Marsh, 1982	6.81 E-3 7.60 E-3	7.19 E-3	

II.C.3. ADDITIONAL COMMENTS (CARCINOGENICITY, INHALATION EXPOSURE)

A geometric mean was obtained for data sets obtained within distinct exposed populations (U.S. EPA, 1984). The final estimate is the geometric mean of those two values. It was assumed that the increase in age-specific mortality rate of lung cancer was a function only of cumulative exposures.

The slope factor in terms of mg absorbed dose/kg bw/day was calculated assuming a 70 kg human body weight, 20 cu.m air inhaled/day and 30% absorption of inhaled arsenic.

The unit risk should not be used if the air concentration exceeds 2 ug/cu.m, since above this concentration the slope factor may differ from that stated.

<<< Arsenic, inorganic >>>

II.C.4. DISCUSSION OF CONFIDENCE (CARCINOGENICITY, INHALATION EXPOSURE)

Overall a large study population was observed. Exposure assessments included air measurements for the Anaconda smelter and both air measurements and urinary arsenic for the ASARCO smelter. Observed lung cancer incidence was significantly increased over expected values. The range of the estimates derived from data from two different exposure areas was within a factor of 6.

------<<< Arsenic, inorganic >>>------

II.D. EPA DOCUMENTATION, REVIEW, AND CONTACTS (CARCINOGENICITY ASSESSMENT)

II.D.1. EPA DOCUMENTATION

U.S. EPA. 1984. Health Assessment Document for Inorganic Arsenic. Environmental Criteria and Assessment Office, Research Triangle Park, NC.

EPA 600/8-83-021F.

II.D.2. REVIEW (CARCINOGENICITY ASSESSMENT)

The 1984 Health Assessment Document for Inorganic Arsenic received Agency and external review including a review by SAB.

Agency Work Group Review: 01/13/88

Verification Date: 01/13/88

II.D.3. U.S. EPA CONTACTS (CARCINOGENICITY ASSESSMENT)

Herman J. Gibb / ORD -- (202)382-5898 / FTS 382-5898

Chao W. Chen / ORD -- (202)382-5898 / FTS 382-5898

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III. HEALTH HAZARD ASSESSMENTS FOR VARIED EXPOSURE DURATIONS

Substance Name -- Arsenic, inorganic
CASRN -- 7440-38-2

Not available at this time

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IV. U.S. EPA REGULATORY ACTIONS

Substance Name -- Arsenic, inorganic
CASRN -- 7440-38-2
Last Revised -- 03/01/88

EPA risk assessments may be updated as new data are published and as assessment methodologies evolve. Regulatory actions are frequently not updated at the same time. Compare the dates for the regulatory actions in this section with the verification dates for the risk assessments in sections I and II, as this may explain inconsistencies. Also note that some regulatory actions consider factors not related to health risk, such as technical or economic feasibility. Such considerations are indicated for each action. In addition, not all of the regulatory actions listed in this section involve enforceable federal standards. Please direct any questions you may have concerning these regulatory actions to the U.S. EPA contact listed for that particular action. Users are strongly urged to read the background information on each regulatory action in Background Document 4 in Service Code 5.

IV.A. CLEAN AIR ACT (CAA)

No data available

------<<< Arsenic, inorganic >>>------

IV.B. SAFE DRINKING WATER ACT (SDWA)

IV.B.1. MAXIMUM CONTAMINANT LEVEL GOAL (MCLG) for Drinking Water

Value (status) -- 0.05 mg/L (Proposed, 1985)

Considers technological or economic feasibility? -- NO

Discussion -- An MCLG of 0.05 mg/L for arsenic is proposed based on the current MCL of 0.05 mg/L. Even though arsenic is potentially carcinogenic in humans by inhalation and ingestion, its potential essential nutrient value was considered in determination of an MCLG. The basis for this evaluation is nutritional requirements by NAS (NAS, 1983, Vol. 5, Drinking Water and Health, National Academy of Sciences Press, Washington, DC.)

Reference -- 50 FR 46936 Part IV (11/13/85)

EPA Contact -- Criteria and Standards Division, ODW / (202)382-7571 / FTS 382-7571; or Drinking Water Hotline / (800)426-4791

<<< Arsenic, inorganic >>>

IV.B.2. MAXIMUM CONTAMINANT LEVEL (MCL) for Drinking Water

Value (status) -- 0.05 mg/L (Interim, 1980)

Considers technological or economic feasibility? -- YES

Discussion -- As an interim measure the U.S. EPA is using the value previously derived by the Public Health Service.

Reference -- 45 FR 57332 (08/27/80)

EPA Contact -- Criteria and Standards Division, ODW / (202)382-7571 / FTS 382-7571; or Drinking Water Hotline / (800)426-4791

------<<< Arsenic, inorganic >>>------

IV.C. CLEAN WATER ACT (CWA)

IV.C.1. AMBIENT WATER QUALITY CRITERIA, Human Health

Water and Fish Consumption -- 2.2E-3 ug/L

Fish Consumption Only -- 1.75E-2 ug/L

Considers technological or economic feasibility? -- NO

Discussion -- For the maximum protection from the potential carcinogenic properties of this chemical, the ambient water concentration should be zero. However, zero may not be attainable at this time, so the recommended criteria represents a E-6 estimated incremental increase of cancer risk over a lifetime.

Reference -- 45 FR 79318 (11/28/80)

EPA Contact -- Criteria and Standards Division, OWRS (202)475-7315 / FTS 475-7315

<<< Arsenic, inorganic >>>

IV.C.2. AMBIENT WATER QUALITY CRITERIA, Aquatic Organisms

Freshwater:

Acute -- 3.6E+2 ug/L (Arsenic III)
Chronic -- 1.9E+2 ug/L (Arsenic III)

Marine:

Acute -- 6.9E+1 ug/L (Arsenic III)
Chronic -- 3.6E+1 ug/L (Arsenic III)

Considers technological or economic feasibility? -- NO

Discussion -- The criteria given are for Arsenic III. Much less data are available on the effects of Arsenic V to aquatic organisms, but the toxicity seems to be less. A complete discussion may be found in the referenced notice.

Reference -- 50 FR 30784 (07/29/85)

EPA Contact -- Criteria and Standards Division, OWRS
(202)475-7315 / FTS 475-7315

------<<< Arsenic, inorganic >>>------

IV.D. FEDERAL INSECTICIDE, FUNGICIDE, AND RODENTICIDE ACT (FIFRA)

No data available

------<<< Arsenic, inorganic >>>------

IV.E. TOXIC SUBSTANCES CONTROL ACT (TSCA)

No data available

------<<< Arsenic, inorganic >>>------

IV.F. RESOURCE CONSERVATION AND RECOVERY ACT (RCRA)

IV.F.1. RCRA APPENDIX IX, for Ground Water Monitoring

Status -- Listed

Reference -- 52 FR 25942 (07/09/87)

EPA Contact -- Jerry Garman / OSW / (202)382-4658 / FTS 382-4658

------<<< Arsenic, inorganic >>>------

IV.G. SUPERFUND (CERCLA)

IV.G.1. REPORTABLE QUANTITY (RQ) for Release into the Environment

Value (status) -- 1 pound (Proposed, 1987)

Considers technological or economic feasibility? -- NO

Discussion -- The proposed 1-pound RQ for arsenic is based on its potential carcinogenicity. Available data indicate a hazard ranking of high based on potency factor of 142.31/mg/kg/day and a weight-of-evidence group A, which corresponds to an RQ of 1 pound. Evidence found in "Water-Related Environmental Fate of 129 Priority Pollutants" (EPA

440/4-79-029a) also indicates that this material, or a constituent of this material, is bioaccumulated to toxic levels in the tissue of aquatic and marine organisms, and has the potential to concentrate in the food chain.

Reference -- 52 FR 8140 (03/16/87)

EPA Contact -- RCRA/Superfund Hotline
(800)424-9346 / (202)382-3000 / FTS 382-3000

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V. SUPPLEMENTARY DATA

Substance Name -- Arsenic, inorganic
CASRN -- 7440-38-2

Not available at this time

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VI. BIBLIOGRAPHY

Substance Name -- Arsenic, inorganic
CASRN -- 7440-38-2
Last Revised -- 09/01/89

VI.A. ORAL RfD REFERENCES

None

------<<< Arsenic, inorganic >>>------

VI.B. INHALATION RfD REFERENCES

None

------<<< Arsenic, inorganic >>>------

VI.C. CARCINOGENICITY ASSESSMENT REFERENCES

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Axelson, O., E. Dahlgren, C.D. Jansson and S.O. Rehnlund. 1978. Arsenic exposure and mortality: A case referent study from a Swedish copper smelter. Br. J. Ind. Med. 35: 8-15.

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Brown, C.C. and K.C. Chu. 1983a. Approaches to epidemiologic analysis of prospective and retrospective studies: Example of lung cancer and exposure to arsenic. In: Risk Assessment Proc. SIMS Conf. on Environ. Epidemiol. June 8-July 2, 1982, Alta, VT. SIAM Publication.

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DiPaolo, J. and B. Casto. 1979. Quantitative studies of in vitro morphological transformation of Syrian hamster cells by inorganic metal salts. Cancer Res. 39: 1008-1013.

Higgins, I. 1982. Arsenic and respiratory cancer amony a sample of Anaconda smelter workers. Report submitted to the Occupational Safety and Health Administration in the comments of the Kennecott Minerals Company on the inorganic arsenic rulemaking. (Exhibit 203-5)

Higgins, I., K. Welch and C. Burchfield. 1982. Mortality of Anaconda smelter workers in relation to arsenic and other exposures. University of Michigan, Dept. Epidemiology, Ann Arbor, MI.

IARC (International Agency for Research on Cancer). 1980. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man, Vol. 23. Some Metals and Metallic Compounds. World Health Organization, Lyon, France.

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Lee-Feldstein, A. 1983. Arsenic and respiratory cancer in man: Follow-up of an occupational study. In: Arsenic: Industrial, Biomedical, and Environmental Perspectives, W. Lederer and R. Fensterheim, Ed. Van Nostrand Reinhold, New York.

Mabuchi, K., A. Lilienfeld and L. Snell. 1979. Lung cancer among pesticide workers exposed to inorganic arsenicals. Arch. Environ. Health. 34: 312-319.

Matanoski, G., E. Landau, J. Tonascia, C. Lazar, E. Elliot, W. McEnroe and K. King. 1981. Cancer mortality in an industrial area of Baltimore. Environ. Res. 25: 8-28.

Morton, W., G. Starr, D. Pohl, J. Stoner, S. Wagner and P. Weswig. 1976. Skin cancer and water arsenic in Lane County, Oregon. Cancer. 37: 2523-2532.

Ohno, H., F. Hanaoka and M. Yamada. 1982. Inductibility of sister chromatid exchanges by heavy-metal ions. Mutat. Res. 104: 141-145.

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Roth, F. 1958. Uber den Bronchialkrebs Arsengeschodigter Winzer. Virchows Arch. 331: 119-137.

Sommers, S.C. and R.G. McManus. 1953. Multible arsenical cancers of the skin and internal organs. Cancer. 6: 347-359.

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Tokudome, S. and M. Kuratsune. 1976. A cohort study on mortality from cancer and other causes among workers at a metal refinery. Int. J. Cancer. 17: 310-317.

Tseng, W.P. 1977. Effects and dose response relationships of skin cancer and blackfoot disease with arsenic. Environ. Health Perspect. 19: 109-119.

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------<<< Arsenic, inorganic >>>------

VI.D. DRINKING WATER HA REFERENCES

None

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SYNONYMS

7440-38-2
Arsenic
Arsenic, inorganic
gray-arsenic

C-8 (b) 1,1-DICHLOROETHANE

The attached "Health Effects Assessment For 1,1-Dichloroethane" (USEPA, 1984b) is provided as a technical summary.

PB86-134384

EPA/540/1-86/027
September 1984

HEALTH EFFECTS ASSESSMENT FOR 1,1-DICHLOROETHANE

U.S. Environmental Protection Agency
Office of Research and Development
Office of Health and Environmental Assessment
Environmental Criteria and Assessment Office
Cincinnati, OH 45268

U.S. Environmental Protection Agency
Office of Emergency and Remedial Response
Office of Solid Waste and Emergency Response
Washington, DC 20460

DISCLAIMER

This report has been funded wholly or in part by the United States Environmental Protection Agency under Contract No. 68-03-3112 to Syracuse Research Corporation. It has been subject to the Agency's peer and administrative review, and it has been approved for publication as an EPA document. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

PREFACE

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with 1,1-dichloroethane. All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered as preliminary and reflect limited resources allocated to this project. Pertinent toxicologic and environmental data were located through on-line literature searches of the Chemical Abstracts, TOXLINE, CANCERLINE and the CHEMFATE/DATALOG data bases. The basic literature searched supporting this document is current up to September, 1984. Secondary sources of information have also been relied upon in the preparation of this report and represent large-scale health assessment efforts that entail extensive peer and Agency review. The following Office of Health and Environmental Assessment (OHEA) sources have been extensively utilized:

U.S. EPA. 1980b. Ambient Water Quality Criteria for Chlorinated Ethanes. Environmental Criteria and Assessment Office, Cincinnati, OH. EPA 440/5-80-029. NTIS PB 81-117624. (Cited in U.S. EPA, 1983b)

U.S. EPA. 1983b. Drinking Water Criteria Document for 1,1-Dichloroethane. Prepared by the Environmental Criteria and Assessment Office, Cincinnati, OH, OHEA for the Office of Drinking Water, Washington, DC. Final draft.

The intent in these assessments is to suggest acceptable exposure levels whenever sufficient data were available. Values were not derived or larger uncertainty factors were employed when the variable data were limited in scope tending to generate conservative (i.e., protective) estimates. Nevertheless, the interim values presented reflect the relative degree of hazard associated with exposure or risk to the chemical(s) addressed.

Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, the AIS or acceptable intake subchronic, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval (i.e., for an interval that does not constitute a significant portion of the lifespan). This type of exposure estimate has not been extensively used or rigorously defined, as previous risk assessment efforts have been primarily directed towards exposures from toxicants in ambient air or water where lifetime exposure is assumed. Animal data used for AIS estimates generally include exposures with durations of 30-90 days. Subchronic human data are rarely available. Reported exposures are usually from chronic occupational exposure situations or from reports of acute accidental exposure.

The AIC, acceptable intake chronic, is similar in concept to the ADI (acceptable daily intake). It is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan [see U.S. EPA (1980a) for a discussion of this concept]. The AIC is route specific and estimates acceptable exposure for a given route with the implicit assumption that exposure by other routes is insignificant.

Composite scores (CSs) for noncarcinogens have also been calculated where data permitted. These values are used for ranking reportable quantities; the methodology for their development is explained in U.S. EPA (1983a).

For compounds for which there is sufficient evidence of carcinogenicity, AIS and AIC values are not derived. For a discussion of risk assessment methodology for carcinogens refer to U.S. EPA (1980a). Since cancer is a process that is not characterized by a threshold, <u>any</u> exposure contributes an increment of risk. Consequently, derivation of AIS and AIC values would be inappropriate. For carcinogens, q_1^*s have been computed based on oral and inhalation data if available.

ABSTRACT

In order to place the risk assessment evaluation in proper context, refer to the preface of this document. The preface outlines limitations applicable to all documents of this series as well as the appropriate interpretation and use of the quantitative estimates.

Toxicological data are limited to subchronic inhalation studies. The U.S. EPA (1983b) has employed these data to estimate an acceptable oral exposure level of 8.1 mg/day which is adopted here as the oral AIC. An inhalation AIC of 9.7 mg/day has been estimated based on subchronic inhalation data. A CS of 9.8 was calculated based on kidney damage in cats exposed for 26 weeks to a TWA level of 750 ppm.

Limited data indicate that 1,1-dichloroethane may have the potential for carcinogenic activity in experimental animals. Data were inadequate for quantitative risk assessment. Additional experimental data are needed in order to adequately address the issue of potential carcinogenicity.

ACKNOWLEDGEMENTS

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LIST OF ABBREVIATIONS

ADI	Acceptable daily intake
AIC	Acceptable intake chronic
AIS	Acceptable intake subchronic
BCF	Bioconcentration factor
bw	Body weight
CAS	Chemical Abstract Service
CNS	Central nervous system
CS	Composite score
K_{ow}	Octanol/water partition coefficient
LOAEL	Lowest-observed-adverse-effect level
MED	Minimum effective dose
NOEL	No-observed-effect level
ppm	Parts per million
RV_d	Dose-rating value
RV_e	Effect-rating value
SGOT	Serum glutamate oxaloacetate transaminase
SGPT	Serum glutamate pyruvate transaminase
STEL	Short-term exposure limit
TLV	Threshold limit value
TWA	Time-weighted average

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1. ENVIRONMENTAL CHEMISTRY AND FATE

The relevant physical and chemical properties and environmental fate of 1,1-dichloroethane (CAS Registry No. 75-34-3), also known as ethylidene chloride or ethylidene dichloride, are given below.

Chemical class:	halogenated aliphatic hydrocarbon
Molecular weight:	98.96
Vapor pressure:	182 mm Hg at 20°C (Archer, 1979)
Water solubility:	5500 mg/ℓ at 20°C (Archer, 1979)
K_{ow}:	61.6 (Valvani et al., 1981)
Soil mobility: (predicted as retardation factor for a soil depth of 140 cm and organic carbon content of 0.087%)	1.2 (estimated)
BCF:	6.6 (estimated)
Half-life in air:	1.5 months (Callahan et al., 1979)
Half-life in water:	1-5 days (estimated)

A soil retardation factor of 1.2 has been estimated for 1,1 dichloroethane using the soil adsorption coefficient and K_{ow} (Schwarzenbach and Westall, 1981). The K_{ow} value for 1,1-dichloroethane (61.6) is intermediate between the K_{ow} values for chloroform (93) and 1,2-dichloroethane (30). The soil retardation factor for a soil depth of 140 cm and organic carbon content of 0.087% is 1.2 for both 1,2-dichloroethane and chloroform (Wilson et al., 1981). Therefore, the retardation factor for 1,1-dichloroethane has been estimated to be 1.2.

The BCF value of 6.6 given above has been estimated from the following equation: $\log BCF = 0.85 \log K_{ow} - 0.70$ (Veith et al., 1979).

The ratio of the reaeration rate constants for 1,1-dichloroethane has been experimentally determined to be 0.71 (Smith et al., 1980). The half-life value has been estimated from this reaeration rate ratio and the oxygen reaeration rates in representative water bodies (0.19-0.96 day^{-1}), with the assumption that the volatilization is a first order process (Mabey et al., 1981).

The half-life value for 1,1-dichloroethane in soil could not be located in the available literature; however, evaporation is expected to be the predominant loss mechanism from the soil surface. The half-life for soil evaporation should be longer than its evaporation half-life from water. In subsurface soil, the loss of 1,1-dichloroethane through biodegradation is expected to be insignificant (Wilson et al., 1983). Therefore, 1,1-dichloroethane may persist in soil and is expected to be removed primarily through leaching into groundwater.

2. ABSORPTION FACTORS IN HUMANS AND EXPERIMENTAL ANIMALS

2.1. ORAL

No studies have been conducted regarding gastrointestinal absorption of 1,1-dichloroethane. Based on similarities of molecular size and lipophilicity as evidenced by olive oil/water partition coefficients (69.2 for 1,1-dichloroethane and 39.8 for 1,2-dichloroethane) (Sato and Nakajima, 1979), it was suggested that gastrointestinal absorption of 1,1-dichloroethane may proceed somewhat faster than absorption of 1,2-dichloroethane. Spreafico et al. (1980) reported rapid absorption of 1,2-dichloroethane in rats after single oral doses of 25 mg/kg bw or 150 mg/kg bw in corn oil.

2.2. INHALATION

No studies regarding the extent or rate of absorption from inhalation of 1,1-dichloroethane have been located. Goldstein et al. (1974) suggested that with gases having a blood/air partition coefficient of $\geq$1.2, respiration is the limiting factor in reaching equilibrium. Sato and Nakajima (1979) reported blood/air coefficients of 4.7 and 19.5 for 1,1- and 1,2-dichloroethane, respectively. Therefore, it might be expected that 1,1-dichloroethane would be absorbed moderately from inhalation exposure, but absorbed less and eliminated more rapidly than 1,2-dichloroethane, which helps explain the observation that the inhalation toxicity of 1,1-dichloroethane is less than the toxicity of 1,2-dichloroethane (Lazarew, 1929).

3. TOXICITY IN HUMANS AND EXPERIMENTAL ANIMALS

3.1. SUBCHRONIC

3.1.1. Oral. Few studies of the effects of subchronic oral administration of 1,1-dichloroethane on animals have been located. In a very limited study, Larson et al. (1955) intubated three mongrel dogs with 200 mg/kg bw 1,1-dichloroethane 6 days/week for 8 weeks to study the effects on the adrenal gland. All three test animals survived the treatment and none had significant histological changes in the adrenals. Other parameters of toxicity were not reported.

Preliminary to conducting a long-term carcinogenesis bioassay in rats and mice, NCI (1978) conducted a subchronic range-finding study by administering 1,1-dichloroethane in corn oil by gavage. Groups of five male and five female Osborne-Mendel rats were given 562, 1000, 1780, 3160 or 5620 mg/kg bw/day 5 days/week for 6 weeks. Male rats in the 1000 and 1780 dose groups and females in the 1780 and 3160 mg/kg/day groups exhibited body weight depression. Mortality occurred in two female rats in the 3160 mg/kg/day group. Groups of five male and five female $B6C3F_1$ mice were treated with 1000, 1780, 3160, 5620 or 10,000 mg/kg/day 5 days/week for 6 weeks. No body weight depression occurred in mice, but mortality occurred in two male and three female mice in the 5620 mg/kg/day dose group. These studies were too limited in their assessment of criteria of toxicity to be useful in risk assessment.

3.1.2. Inhalation. In a subchronic inhalation study, Hofmann et al. (1971) exposed groups of 10 rats, 4 cats, 4 rabbits and 10 guinea pigs to 500 ppm (~2025 mg/m³) 1,1-dichloroethane 6 hours/day, 5 days/week for 13 weeks. No effects were reported in any of the animals tested. Exposure to 1000 ppm (~4050 mg/m³) 6 hours/day, 5 days/week using the same test animals continued for another 13 weeks. The most sensitive animal tested appeared to be the cat, the only animal in which adverse effects were noted. Blood urea nitrogen levels were immediately elevated and rose steadily to week 24, at which time they peaked at ~3 times the control levels. Blood creatinine levels showed a parallel but less dramatic increase. No increase of SGOT or SGPT was noted. Histopathological examination of the cats revealed renal tubular dilatation and degeneration, indicating renal damage.

Torkelson and Rowe (1981) summarized an unpublished subchronic inhalation study by Dow Chemical Company in which unspecified numbers of rats, guinea pigs, rabbits and dogs were exposed to 500 or 1000 ppm (2025 or 4050 mg/m^3, respectively) 1,1-dichloroethane for 7 hours/day, 5 days/week for 6 months. Blood chemistries, necropsy and histological examinations revealed no changes attributed to the exposure. Based on the studies by Torkelson and Rowe (1981) and Hoffman et al. (1971), a NOEL of 500 ppm (2025 mg/m^3) can be suggested for subchronic inhalation exposure to 1,1-dichloroethane in rats, cats, rabbits, guinea pigs and dogs.

3.2. CHRONIC

3.2.1. Oral. The only study of chronic oral toxicity to 1,1-dichloroethane was reported in the NCI carcinogenicity assay (NCI, 1978). Groups of 50 male and 50 female Osborne-Mendel rats and $B6C3F_1$ mice were intubated with 1,1-dichloroethane in corn oil. Control and vehicle control groups consisted of 20 male and 20 female animals of each species. Treatments were administered 5 days/week for 3 weeks, followed by 1 dose-free week and 3 additional treatment weeks over the 78-week treatment period. The following time weighted dosages for treatment days were obtained: male rats, high-dose group 764 mg/kg bw/day, low-dose group 382 mg/kg bw/day; female rats, high-dose group 950 mg/kg bw/day, low-dose group 475 mg/kg bw/day. Mice were treated 5 days/week for 78 weeks with the dosage increased after 6 weeks and again after 9 weeks. The TWA doses for treatment days for male mice were 2885 and 1442 mg/kg bw/day for low- and high-dose groups, respectively; for female mice, these doses were 3331 and 1665 mg/kg bw/day, respectively. Rats were observed for an additional 33 weeks and mice for an additional 13 weeks, after which survivors were killed. All animals that died or were killed when moribund or at the conclusion of the observation period were subjected to necropsy.

For both male and female rats, body weight curves for treatment and vehicle control groups were similar and somewhat below untreated controls. All groups of rats exhibited a hunched appearance, abdominal urine stains, labored breathing, wheezing and nasal discharge. By the conclusion of the trial, all surviving rats exhibited these signs, though the incidence early in the study appeared to be slightly higher in the treatment groups. Mortality was high in both male and female groups of rats and appeared to be slightly higher in 1,1-dichloroethane-exposed groups, though no significantly greater mortality was observed in the high-dose groups. Chronic murine pneumonia and kidney inflammation accounted for the vast majority of mortality among both control and treatment groups.

Body weight curves for male and female mice seemed unaffected by treatment or vehicle; there appeared to be no definitive signs of 1,1-dichloroethane toxicity in physical appearance or behavior throughout the study. Examination of statistically predicted survival curves indicated that survival of both male and female mice had been adversely affected by the high dose of 1,1-dichloroethane, although no specific pathological lesions were observed at significantly higher incidences in treated groups. Because of the increased mortality associated with treatment, no NOEL or LOAEL was defined by this study for mice.

3.2.2. Inhalation. No pertinent data concerning chronic inhalation exposure to 1,1-dichloroethane could not be located in the available literature.

3.3. TERATOGENICITY AND OTHER REPRODUCTIVE EFFECTS

3.3.1. Oral. Pertinent data regarding teratogenicity or reproductive dysfunction in humans or animals associated with ingestion of 1,1-dichloroethane could not be located in the available literature.

3.3.2. Inhalation. Pertinent data regarding teratogenicity or reproductive dysfunction in humans related to inhalation exposure to 1,1-dichloroethane could not be located in the available literature. Schwetz et al. (1974) exposed rats to 0, 3800 or 6000 ppm 1,1-dichloroethane for 7 hours/day on days 5-15 of gestation. A significantly increased incidence of delayed ossification of sternebrae resulted from exposure to 6000 ppm 1,1-dichloroethane. Assuming a body weight of 0.35 kg and an inhalation rate of 0.26 m^3/day for rats, exposure to 3800 ppm for 7 hours/day, corresponding to an intake of ~3333 mg/kg/day, was found to be a NOEL in this study. Because this intake (~3333 mg/kg/day) is greater than the intake (269 mg/kg/day) calculated for rats in the study by Hofmann et al. (1971), the Schwetz et al. (1974) study will not impact risk assessment.

3.4. TOXICANT INTERACTIONS

Pertinent data on the toxic interactions of 1,1-dichloroethane with other xenobiotics could not be located in the available literature; however, it can be anticipated that exposure to other agents which deplete glutathion would enhance its toxicity.

3.5. HEALTH EFFECTS IN HUMANS

Limited information is available concerning the effects of 1,1-dichloroethane on humans. At one time the compound was used as an anesthetic, with an anesthetic pressure of 0.026 atmospheres, ~105,000 mg/m^3 (Miller et al., 1965). The ability of the compound to induce cardiac arrhythmias caused discontinuation of its use as an anesthetic (Browning, 1965). It is probable that human exposure to sufficiently high levels would cause CNS depression and respiratory tract and skin irritation, since many other chlorinated aliphatics do (Parker et al., 1979). No dose-response data concerning these phenomena are available.

4. CARCINOGENICITY

4.1. HUMAN DATA

Pertinent data concerning the carcinogenicity of 1,1-dichloroethane in humans could not be located in the available literature.

4.2. BIOASSAYS

The only carcinogenicity bioassay concerning 1,1-dichloroethane located in the available literature was conducted by NCI (1978). The protocol and noncarcinogenic data generated by this study were discussed in Section 3.2. Under the conditions of this study, male rats showed no significant change in the incidence of neoplasia which were compound related. Female rats (Table 4-1) showed a significant dose-response relationship in the incidence of hemangiosarcoma when measured by the Cochran-Armitage test for linear trend in proportions comparing the two dose groups with either the matched vehicle control ($p=0.041$) or the pooled vehicle control groups ($p=0.021$). By the Cochran-Armitage test, a significant ($p=0.043$) dose-related incidence of mammary adenocarcinomas was also observed. Results of the Fisher Exact test showed no significant incidence of either of these tumors. Because of high mortality early in the study, statistical analysis of data only from survivors of ≥ 1 year of exposure was also performed. Using the Cochran-Armitage test, statistical significance ($p=0.034$) was demonstrated only for mammary adenocarcinoma in female rats. Results using the Fisher Exact test were statistically negative.

In male mice surviving ≥ 1 year, the Cochran-Armitage test demonstrated a significant ($p=0.016$) dose-related incidence of hepatocellular carcinoma compared with pooled vehicle controls. Using the Fisher Exact test, a probability level of $p=0.027$ was calculated by comparing high dose and pooled vehicle control groups. Applying the Bonferroni criterion, which

TABLE 4-1

Summary of Incidence of Statistically Significant Primary Tumors in Osborne-Mendel Rats and $B6C3F_1$ Mice[a,b]

Species	Tumor Type	Pooled Vehicle Control	Matched Vehicle Control	Low Dose	High Dose
Female rats p values[c]	mammary adenocarcinoma	1/39 (0.03) NS	0/19 (0.00) p=0.043	1/50 (0.02) NS	5/50 (0.10) NS
Female rats p values[c]	hemangiosarcoma	0/39 (0.00) p=0.021	0/19 (0.00) p=0.041	0/50 (0.00) NS	4/50 (0.08) NS
Female rats surviving >52 weeks p values[c]	mammary adenocarcinomas	NR	0/16 (0.00) p=0.034	1/28 (0.04) NS	5/31 (0.16) NS
Female mice p values[c]	endometrial stromal polyp	0/79 (0.00) p=0.005	0/20 (0.00) p=0.036	0/47 (0.00) NS	4/46 (0.09) p=0.017*
Male mice surviving >52 weeks p values[c]	hepatocellular carcinoma	6/72 (0.08) p=0.016	1/19 (0.05) NS	8/48 (0.17) NS	8/32 (0.25) p=0.027*,d

[a]Source: NCI, 1978

[b]Experimental design summarized in text

[c]The probability level for the Cochran-Armitage test is given beneath the incidence of tumors in the corresponding control group when p<0.05; otherwise, not significant (NS) is indicated. The probability level for the Fisher Exact test for the comparison of a treated group with a control group is given beneath the incidence of tumors in that treated group when p<0.05; the asterisk (*) indicates comparison of the treated group with the pooled vehicle control group.

[d]The Fisher Exact test probability level of p=0.027 was marginal and not considered significant under the Bonferroni criterion.

NR = Not reported; NS = Not significant

requires that the normally accepted level of statistical significance ($p<0.05$) be divided by the number of dose levels (2), resulted in an acceptable p value of <0.025 for statistical significance. By this criterion, the incidence of hepatocellular carcinoma in the high dose group was considered to be marginal and not statistically different from the incidence in the pooled vehicle control group.

In female mice, the Cochran-Armitage test showed a significantly positive dose-response relationship in the incidence of benign endometrial stromal polyps when compared with the matched vehicle control ($p=0.036$) or pooled vehicle control ($p=0.005$) groups. By the Fisher Exact test, the incidence of endometrial stromal polyps in the high groups was significantly ($p=0.017$) higher than in pooled vehicle controls.

Based on the results of statistical analysis and the low survival of all groups, the NCI (1978) concluded that "these findings are indicative of the possible carcinogenic potential of the test compound. However, ... there was no conclusive evidence for the carcinogenicity of 1,1-dichloroethane in Osborne-Mendel rats or $B6C3F_1$ mice."

4.3. OTHER RELEVANT INFORMATION

4.3.1. Mutagenicity Tests. Simmon et al. (1977) tested the mutagenic activity of several chemicals identified in drinking water in the Ames _Salmonella_ _typhimurium_/microsomal activation assay. Doses of the chemicals ranged up to 5 mg/plate. Negative results were reported for 1,1-dichloroethane in _S_. _typhimurium_ strains TA1535, TA1537, TA1538, TA98 and TA100, although the specific dose of 1,1-dichloroethane used and corresponding plate counts were not specified.

Nesnow (1982) reported a positive response of 1,1-dichloroethane in an enhanced viral transformation assay in Syrian hamster embryo cells, using the methods of Hatch et al. (1982). Details of protocol were not reported.

4.4. WEIGHT OF EVIDENCE

The only bioassay of the carcinogenicity of 1,1-dichloroethane located was the NCI (1978) bioassay described previously. High mortality among all groups probably precluded significant occurrence of tumors related to long-term exposure. Weisburger (1977) reviewed NCI bioassays of several halogenated aliphatics and noted striking similarities in the types of tumors produced. An example was the formation of hepatocellular carcinoma induced in mice by 1,1-dichloroethane and tetrachloroethylene. Although the incidence of hepatocellular carcinoma in mice exposed to 1,1-dichloroethane was not significant (see Section 4.2.), the similarity in lesions produced by other halogenated aliphatics raises a concern that the marginal results obtained with 1,1-dichloroethane are biologically, if not statistically, significant. Nevertheless, neither IARC nor the Carcinogen Assessment Group of the U.S. EPA has officially classified 1,1-dichloroethane as to carcinogenicity, based presumably on a lack of evidence for human carcinogenicity and the marginal signficance of the NCI bioassay which is considered to be limited evidence for animal carcinogenicity. Applying the criteria for evaluating weight of evidence proposed by the Carcinogen Assessment Group (Federal Register, 1984), 1,1-dichloroethane is most appropriately classified a Group D-Not Classified chemical.

5. REGULATORY STANDARDS AND CRITERIA

Table 5-1 lists the various regulatory standards and criteria for 1,1-dichloroethane.

The ACGIH (1980) recommended a TWA-TLV of 200 ppm (~810 mg/m³) for occupational exposure to 1,1-dichloroethane, with a STEL of 250 ppm (~101 mg/m³). This recommendation is based in part on the data of Hofmann et al. (1971) and the unpublished data of the Dow Chemical Company cited in Torkelson and Rowe (1981) (see Chapter 3). The current OSHA standard for occupational exposure to 1,1-dichloroethane is 100 ppm (~405 mg/m³), but no NIOSH criterion for occupational exposure exists (Parker et al., 1979).

In discussing the derivation of ambient water quality criteria for chlorinated ethanes, the U.S. EPA (1980b) concluded that "insufficiency in the available data" precluded establishment of a satisfactory criterion for 1,1-dichloroethane. The nature of the deficiencies in the data was not discussed. In a subsequent review (U.S. EPA, 1983b), an ADI of 8.1 mg/day for a 70 kg man was proposed. This estimate was based on the NOEL of 2025 mg/m³ defined in Hofmann et al. (1971) and employed a rat 24-hour breathing volume of 0.22 m³/day, an absorption coefficient of 0.5 and an uncertainty factor of 1000.

No currently available information described human populations that may be particularly sensitive to 1,1-dichloroethane. The U.S. EPA (1980b, 1983b) stated that no information was available on unusual sensitivity of any groups to any of the chlorinated ethanes. The U.S. EPA (1980b) suggested, however, that individuals with liver insufficiency or exposure to other hepatotoxins may be at increased risk. Presumably, individuals with impaired renal function may also be unusually sensitive to exposure to 1,1-dichloroethane.

TABLE 5-1

Regulatory Standards and Criteria

Criterion	Standard	Reference
TLV	200 ppm (~810 mg/m³)	ACGIH, 1980
STEL	250 ppm (~1010 mg/m³)	ACGIH, 1980
OSHA	100 ppm (~405 mg/m³)	Parker et al., 1979

6. RISK ASSESSMENT

Risk assessment data for 1,1-dichloroethane are presented in the Appendix to this report.

6.1. ACCEPTABLE INTAKE SUBCHRONIC (AIS)

6.1.1. Oral. Only two reports were located regarding subchronic oral exposure in animals. These reports and their limitations were discussed in Section 3.1. Because of the limited scope of these studies, it was not possible to derive a maximum tolerable daily dose for subchronic oral exposure. However, U.S. EPA (1983b) has used the subchronic inhalation data of Hofmann et al. (1971) to estimate acceptable oral exposure. Using their approach, this study defines a NOEL for rats in units of mg/kg/day as follows:

$$\text{NOEL} = \frac{(2025\ \text{mg/m}^3)\ (0.22\ \text{m}^3\text{/day})\ (0.5)\ (6\ \text{hr/24 hr})\ (5\ \text{days/7 days})}{0.35\ \text{kg}}$$

$$= 115\ \text{mg/kg/day}$$

The value of 0.22 m^3/day represents the default 24-hour rat breathing volume employed, 0.5 represents the assumed absorption coefficient and 0.35 kg the default rat body weight. Multiplying by 70 kg and dividing by an uncertainty factor of 100 (10 for interspecies variability and 10 for inter-individual variability) results in an estimated AIS of 81 mg/day.

6.1.2. Inhalation. *Reports of two subchronic inhalation studies of* 1,1-dichloroethane in animals were discussed in Section 3.1. The study by Hofmann et al. (1971) demonstrated a NOEL of 500 ppm (~2025 mg/m^3) in rats, cats, rabbits and guinea pigs when exposed for 6 hours/day, 5 days/ week for 13 weeks. After this exposure schedule, the 1,1-dichloroethane concentration was increased to 1000 ppm (4050 mg/m^3) for an additional 13 weeks. The 1000 ppm level also represented a NOEL for all test animals except cats in which elevated blood urea nitrogen was detected and adverse histologic changes in the kidney observed. For the cat, 1000 ppm represents a LOAEL. An unpublished subchronic inhalation study conducted by Dow Chemical Company and summarized by Torkelson and Rowe (1981) supports the NOEL suggested by the earlier study.

Estimated inhaled doses may be calculated for each exposed species and will vary in accordance with the ratio of ventilation volume/time to body weight. Estimates of ventilation volume are rough estimates since these values are particularly sensitive to experimental conditions and manipulations. The estimated animal doses are presented in Table 6-1. Since the cat data provide the most protective dose estimate (138 mg/kg/day), this dose is chosen as a starting point for the AIS estimate. Assuming a human body weight of 70 kg and applying an uncertainty factor of 100 results in an AIS of 96.6 mg/day.

A CS for 1,1-dichloroethane was calculated based on the kidney damage observed by Hofmann et al. (1971) in cats exposed to 500 ppm for 13 weeks and 1000 ppm for an additional 13 weeks. An RV_e of 7 was chosen for the effects on the kidneys because there was histologic evidence of kidney damage with demonstrable decrement in organ functions (i.e., elevated blood urea nitrogen). A human MED was calculated by expanding the TWA exposure, 750 ppm, from 6-24 hours/day and from 5-7 days/week. It was also assumed that humans inhale 20 m^3 of air/24 hours and that 1,1-dichloroethane absorption is 50%. An uncertainty factor of 10 was applied to convert from subchronic to chronic data resulting in a human MED of 542 mg/day, which corresponds to an RV_d of 1.4. A CS of 9.8, the product of RV_d and RV_e, is calculated.

TABLE 6-1

Calculated Animal Dose in mg/kg/day[a]

Species	Inhalation Rate (m^3/day)[b]	Body Weight (kg)[b]	Dose in mg/kg bw/day	
			2025 mg/m^3	4050 mg/m^3
Rats	0.22	0.35	227	455
Cats	1.26	3.3	138	276
Rabbits	1.6	1.13	512	1024
Guinea pigs	0.23	0.43	193	387

[a]Source: Hofmann et al., 1971

[b]Estimated inhalation rates and body weights

6.2. ACCEPTABLE INTAKE CHRONIC (AIC)

6.2.1. Oral. The only report of chronic oral exposure to 1,1-dichloroethane was the NCI (1978) bioassay discussed in Section 3.2. As noted before, animals in both dosage levels and control groups experienced pronounced early mortality. Although not statistically significant, some potentiation of mortality in rats appeared to be related to treatment. U.S. EPA (1983b) has used the subchronic inhalation data for the rat from Hofmann et al. (1971) to develop an ADI. It is suggested that their estimate be used for the AIC. The basis for the proposed AIC of 8.1 mg/day is explained in Section 6.1.1. with the addition of an uncertainty factor of 10 (combined uncertainty factor of 1000) to extrapolate from subchronic to chronic exposure.

6.2.2. Inhalation. No reports of chronic inhalation exposure of humans or animals to 1,1-dichloroethane could not be located in the available literature. The ACGIH (1980) recommended a TLV of 200 ppm, based on the studies by Hofmann et al. (1971) and Dow Chemical Company (n.d.), while the OSHA standard for occupational exposure to 1,1-dichloroethane is a TLV of 100 ppm. The TLV of 100 ppm could be used to estimate acceptable exposure, using an uncertainty factor of 10. The uncertainty factor of 10 is used to protect especially sensitive members of populations.

Calculation of the dose is as follows: The TLV (405 mg/m^3) x 10 m^3 inhaled/workday x (5 workdays ÷ 7 days/week) ÷ 10 (UF) = 289 mg/day. The AIC derived from the TLV is ~3-fold higher than the interim AIS derived for subchronic exposure. The discrepancy may reflect differences and uncertainties in the methodologies for obtaining TLVs and calculating acceptable intakes from animal data, or species differences in sensitivity between cats and humans to the toxicity of 1,1-dichloroethane. It is proposed that the more protective approach to AIC development be employed.

Starting with the AIS of 96.6 mg/day and applying an additional uncertainty factor of 10 to extrapolate from subchronic to chronic exposure results in an AIC of 9.7 mg/day. This value should be reevaluated when additional data are available.

6.3. CARCINOGENIC POTENCY (q_1*)

6.3.1. Oral. Results of the NCI (1978) bioassay of 1,1-dichloroethane suggested that this compound may have carcinogenic properties. The significant positive treatment-response associations elucidated by the Cochran-Armitage test for hemangiosarcoma and mammary adenoma in female rats are not necessarily invalidated by the negative results of the Fisher exact test. Heavy mortality among the control groups as well as the treatment groups and application of the Bonferroni criterion undoubtedly contributed to the lack of statistical significance of the Fisher exact test. The heavy mortality among treatment groups probably resulted in underestimating the true carcinogenic potential of 1,1-dichloroethane, especially in light of the positive treatment-response association manifest by the Cochran-Armitage test. Furthermore, as pointed out by Weisburger (1977) (see Section 4.4.), striking similarities in the types of tumors produced by other chlorinated aliphatics are suggestive of a carcinogenic role for 1,1-dichloroethane.

Nonetheless, as indicated by the review panel for the NCI (1978) bioassay on 1,1-dichloroethane, the compound should be retested to resolve the issue of carcinogenicity. Heavy mortality among both treatment and control groups precluded using the data from this study to generate unit carcinogenic risk estimates. Also, the physical condition of the animals was markedly stressed and did not appoximate a normal human population.

6.3.2. Inhalation. Pertinent data regarding the carcinogenicity of 1,1-dichloroethane could not be located in the available literature.

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APPENDIX

Summary Table for 1,1-Dichloroethane

	Species	Experimental Dose/Exposure	Effect	Acceptable Intake (AIS or AIC)	Reference
Inhalation					
AIS	cat	500 ppm ($2025\ mg/m^3$)	none	96.6 mg/day	Hofmann et al., 1971
AIC	cat	500 ppm ($2025\ mg/m^3$)	none	9.7 mg/day	Hofmann et al., 1971
Maximum composite score	cat	TWA 750 ppm 6 hours/day, 5 days/week for 26 weeks ($RV_d = 1.4$)	kidney damage, elevated blood urea nitrogen ($RV_e = 7$)	9.8	Hofmann et al., 1971
Oral					
AIS	rat	500 ppm ($2025\ mg/m^3$)	none	81 mg/day	Hofmann et al., 1971
AIC	rat	500 ppm* ($2025\ mg/m^3$)	none	8.1 mg/day	Hofmann et al., 1971; U.S. EPA, 1983b

*Based on inhalation data as proposed by U.S. EPA (1983b)

C-8 (c) 1,2-DICHLOROETHENE (TOTAL)

The attached Integrated Risk Information System (IRIS) printout (March 1990) is provided as a technical summary.

trans-1,2-Dichloroethylene; CASRN 156-60-5 (01/01/89)

Health risk assessment information on a chemical is included in IRIS only after a comprehensive review of chronic toxicity data by work groups composed of U.S. EPA scientists from several Program Offices. The summaries presented in Sections I and II represent a consensus reached in the review process. The other sections contain U.S. EPA information which is specific to a particular EPA program and has been subject to review procedures prescribed by that Program Office. The regulatory actions in Section IV may not be based on the most current risk assessment, or may be based on a current, but unreviewed, risk assessment, and may take into account factors other than health effects (e.g., treatment technology). When considering the use of regulatory action data for a particular situation, note the date of the regulatory action, the date of the most recent risk assessment relating to that action, and whether technological factors were considered. Background information and explanations of the methods used to derive the values given in IRIS are provided in the five *Background Documents* in Service Code 5, which correspond to Sections I through V of the chemical files.

STATUS OF DATA FOR trans-1,2-Dichloroethylene

File On-Line 09/26/88

Category (section)	Status	Last Revised
Oral RfD Assessment (I.A.)	on-line	01/01/89
Inhalation RfD Assessment (I.B.)	no data	
Carcinogenicity Assessment (II.)	no data	
Drinking Water Health Advisories (III.A.)	no data	
U.S. EPA Regulatory Actions (IV.)	no data	
Supplementary Data (V.)	no data	

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I. CHRONIC HEALTH HAZARD ASSESSMENT FOR NONCARCINOGENIC EFFECTS

Substance Name -- trans-1,2-Dichloroethylene

CASRN -- 156-60-5
Last Revised -- 01/01/89

The Reference Dose (RfD) is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis, but may not exist for other toxic effects such as carcinogenicity. In general, the RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Please refer to Background Document 1 in Service Code 5 for an elaboration of these concepts. RfDs can also be derived for the noncarcinogenic health effects of compounds which are also carcinogens. Therefore, it is essential to refer to other sources of information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file when a review of that evaluation is completed.

<<< trans-1,2-Dichloroethylene >>>

I.A. REFERENCE DOSE FOR CHRONIC ORAL EXPOSURE (RfDo)

I.A.1. ORAL RfD SUMMARY

Critical Effect	Experimental Doses*	UF	MF	RfD
Increased serum alkaline phosphatase in male mice	NOAEL: 0.1 mg/L (17 mg/kg/day)	1000	1	2E-2 mg/kg/day
90-Day Mouse Drinking Water Study	LOAEL: 1 mg/L (175mg/kg/day)			
Barnes et al., 1985				

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*Conversion Factors: See text.

<<< trans-1,2-Dichloroethylene >>>

I.A.2. PRINCIPAL AND SUPPORTING STUDIES (ORAL RfD)

Barnes, D.W., V.M. Sanders, K.L. White, Jr., et al. 1985. Toxicology of trans-1,2-dichloroethylene in the mouse. Drug Chem. Toxicol. 8: 373-392.

Male and female CD-1 mice were given trans-1,2-dichloroethylene (DCE) in their drinking water for 90 days at concentrations of 0.1, 1.0, or 2.0 mg/mL. Based on fluid consumption, the doses were: males - 17, 175, or 387 mg/kg/day and females - 23, 224, or 452 mg/kg/day. There were no differences in fluid consumption among the various groups of mice and at the termination of the 90-day experiment, no DCE-induced changes in terminal body weight or gross pathology were noted in either sex at any dose level. In male mice (N=24), there were significant increases in serum alkaline phosphatase levels at the 175 and 387 mg/kg/day levels. In addition, liver glutathione concentrations were decreased at the highest dose. In females (N=24), the thymus weight, calculated as percent body weight, was significantly decreased at either 224 or 452 mg/kg/day, while the lung weight was depressed at the highest dose only. The levels of serum glutamic-pyruvic (SGPT) and glutamic-oxaloacetic (SGOT) transaminases were decreased at the two higher doses. In addition, the levels of aniline hydroxylase were decreased at all three dose levels, but the levels of cytochromes P-450 and b5, microsomal protein and aminopyrine N-demethylase were not affected by any dose of DCE. Since there is uncertainty about the toxicological significance of the decreases in SGOT, SGPT, and aniline hydroxylase, these parameters will not be used to set RfD values.

The immunotoxicity of trans-1,2-dichloroethylene (DCE) was assessed in a 90-day study by Shopp et al. (1985). Humoral immune status was assessed by measuring: 1) quantitation of spleen IgM antibody forming cells (AFC), 2) hemagglutination titers to sheep erythrocytes (sRBC), and 3) spleen response to the B cell mutagen lipopolysaccharide (LPS). Cell-mediated immunity was assayed by: 1) delayed type hypersensitivity (DTH) to SRBC, 2) popiteal lymph node proliferation in response to SRBC, and 3) spleen cell response to challenge with concanavalin A. In males on day 4 after treatment, there was a significant decrease in AFC/spleen at 17, 175, and 387 mg/kg/day does levels, but the decreases were only significant at the 175 and 387 mg/kg/day levels when the data were calculated on the basis of spleen cells. On day 5, a decrease in AFC was noted only at the 387 mg/kg/day level. No dose-dependent effects were noted in the DCE-treated female mice. In both sexes, there were no changes in hemagglutination titers after DCE treatment and spleen responsiveness to LPS was unaltered in male mice. However, females exposed to 452 mg/kg/day did have an enhanced response to LPS. In addition, lymphocyte responsiveness in the absence of the mitogen (LPS) was decreased at the 224 and 452 mg/kg/day doses in females only. In the cell-mediated immunity assays, there were no dose-related decreases seen in either sex. The significance of the decrease in AFC/spleen in male mice at all three dose levels is uncertain. This decrease is seen at only the 175 and 387 mg/kg/day levels when the data were calculated on the basis of spleen cells. Furthermore, two other measures of humoral immune status, hemagglutination titers and spleen cell response to LPS, were not affected. Accordingly, this parameter will not be used to set a RfD, but will be used as supportive data.

<<< trans-1,2-Dichloroethylene >>>

I.A.3. UNCERTAINTY AND MODIFYING FACTORS (ORAL RfD)

UF = 1000. The UF of 1000 allows for uncertainty in the extrapolation of dose levels from laboratory animals to humans (10A), uncertainty in the threshold for sensitive humans (10H), and uncertainty in the effect of duration when extrapolating from subchronic to chronic exposure (10S).

MF = 1.

I.A.4. ADDITIONAL COMMENTS (ORAL RfD)

CD rats, 22 to 30 days old, were given trans-1,2-dichloroethylene (DCE) for 90 days in their drinking water at doses of 402, 1311 or 3114 mg/kg/day for males and 353, 1257 or 2809 mg/kg/day for females (Hayes et al., 1987). The authors found no compound-related effects on fluid consumption, body weights, hematology, serum chemistry or urinalyses. They did note a significant dose-dependent decrease in kidney weight at the 257 and 2809 mg/kg/day doses in female rats.

Wistar rats were exposed to air containing trans-1,2-dichloroethylene at 0, 200, 1000 or 2000 ppm (0 to 7940 mg/cu.m) (Freundt et al., 1977). Brief (8-hour) or prolonged (8 hours/day, 5 days/week for 1, 2, 8, or 16 weeks) exposure at 200 ppm produced slight degeneration of the liver lobule and lipid accumulation in the Kupffer cells. At 8 and 16 weeks of exposure, severe pneumonic infiltration was observed. Exposure at 1000 ppm for 8 hours resulted in significant reductions in serum albumin, urea nitrogen and alkaline phosphatase. Eight-hour exposures at both 200 and 1000 ppm produced a significant decrease in the number of leucocytes.

<<< trans-1,2-Dichloroethylene >>>

I.A.5. CONFIDENCE IN THE ORAL RfD

Study: Medium
Data Base: Low
RfD: Low

The principal study was well-designed, except for dose spacing, and did establish both a NOEL and LOAEL. The data base confidence is rated low because of the lack of chronic studies and the lack of data on reproductive and developmental toxicity. Confidence in the RfD is rated low because of the data base weakness.

I.A.6. EPA DOCUMENTATION AND REVIEW OF THE ORAL RfD

The only U.S. EPA documentation at present is on IRIS.

Agency RfD Work Group Review: 04/20/88

Verification Date: 04/20/88

I.A.7. EPA CONTACTS (ORAL RfD)

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------<<< trans-1,2-Dichloroethylene >>>------

I.B. REFERENCE DOSE FOR CHRONIC INHALATION EXPOSURE (RfDi)

Not available at this time

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II. CARCINOGENICITY ASSESSMENT FOR LIFETIME EXPOSURE

Substance Name -- trans-1,2-Dichloroethylene
CASRN -- 156-60-5

This chemical has not been evaluated by the U.S. EPA for evidence of human carcinogenic potential.

III. HEALTH HAZARD ASSESSMENTS FOR VARIED EXPOSURE DURATIONS

Substance Name -- trans-1,2-Dichloroethylene
CASRN -- 156-60-5

Not available at this time

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IV. U.S. EPA REGULATORY ACTIONS

Substance Name -- trans-1,2-Dichloroethylene
CASRN -- 156-60-5

Not available at this time

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V. SUPPLEMENTARY DATA

Substance Name -- trans-1,2-Dichloroethylene
CASRN -- 156-60-5

Not available at this time

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VI. REFERENCES

Substance Name -- trans-1,2-Dichloroethylene
CASRN -- 156-60-5

Not available at this time

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SYNONYMS

156-60-5
acetylene dichloride, trans-
dichloroethylene, trans-
1,2-Dichloroethylene, trans-
ethylene, 1,2-dichloro-, (E)-
RCRA waste number U079
trans-acetylene dichloride
trans-dichloroethylene
trans-1,2-Dichloroethylene

C-8 (d) ETHYLBENZENE

The attached Integrated Risk Information System (IRIS) printout (March 1990) is provided as a technical summary.

Ethylbenzene; CASRN 100-41-4 (08/01/89)

Health risk assessment information on a chemical is included in IRIS only after a comprehensive review of chronic toxicity data by work groups composed of U.S. EPA scientists from several Program Offices. The summaries presented in Sections I and II represent a consensus reached in the review process. The other sections contain U.S. EPA information which is specific to a particular EPA program and has been subject to review procedures prescribed by that Program Office. The regulatory actions in Section IV may not be based on the most current risk assessment, or may be based on a current, but unreviewed, risk assessment, and may take into account factors other than health effects (e.g., treatment technology). When considering the use of regulatory action data for a particular situation, note the date of the regulatory action, the date of the most recent risk assessment relating to that action, and whether technological factors were considered. Background information and explanations of the methods used to derive the values given in IRIS are provided in the five Background Documents in Service Code 5, which correspond to Sections I through V of the chemical files.

STATUS OF DATA FOR Ethylbenzene

File On-Line 01/31/87

Category (section)	Status	Last Revised
Oral RfD Assessment (I.A.)	on-line	03/01/88
Inhalation RfD Assessment (I.B.)	no data	
Carcinogenicity Assessment (II.)	on-line	09/07/88
Drinking Water Health Advisories (III.A.)	on-line	03/01/88
U.S. EPA Regulatory Actions (IV.)	on-line	03/01/88

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_I. CHRONIC HEALTH HAZARD ASSESSMENT FOR NONCARCINOGENIC EFFECTS

Substance Name -- Ethylbenzene
CASRN -- 100-41-4
Last Revised -- 03/01/88

The Reference Dose (RfD) is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis, but may not exist for other toxic effects such as carcinogenicity. In general, the RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Please refer to Background Document 1 in Service Code 5 for an elaboration of these concepts. RfDs can also be derived for the noncarcinogenic health effects of compounds which are also carcinogens. Therefore, it is essential to refer to other sources of information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file when a review of that evaluation is completed.

<<< Ethylbenzene >>>

__I.A. REFERENCE DOSE FOR CHRONIC ORAL EXPOSURE (RfDo)

___I.A.1. ORAL RfD SUMMARY

Critical Effect	Experimental Doses*	UF	MF	RfD
Liver and kidney toxicity Rat Subchronic to Chronic Oral Bioassay Wolf et al., 1956	NOEL: 136 mg/kg/day (converted to 97.1 mg/kg/day) LOAEL: 408 mg/kg/day (converted to 291 mg/kg/day)	1000	1	1E-1 mg/kg/day

*Dose Conversion Factors & Assumptions: 5 days/7 days; thus, 136 mg/kg/day x 5 days/7 days = 97.1 mg/kg/day

<<< Ethylbenzene >>>

___I.A.2. PRINCIPAL AND SUPPORTING STUDIES (ORAL RfD)

Wolf, M.A., V.K. Rowe, D.D. McCollister, R.L. Hollingsworth and F. Oyen. 1956. Toxicological studies of certain alkylated benzenes and benzene. Arch. Ind. Health. 14: 387-398.

The chosen study is a rat 182-day oral bioassay in which ethylbenzene was given 5 days/week at doses of 13.6, 136, 408, or 680 mg/kg/day in olive oil gavage. There were 10 albino female rats/dose group and 20 controls.

The criteria considered in judging the toxic effects on the test animals were growth, mortality, appearance and behavior, hematologic findings, terminal concentration of urea nitrogen in the blood, final average organ and body weights, histopathologic findings, and bone marrow counts. The LOAEL of 408 mg/kg/day is associated with histopathologic changes in liver and kidney.

___I.A.3. UNCERTAINTY AND MODIFYING FACTORS (ORAL RfD)

UF = 1000. The uncertainty factor of 1000 reflects 10 for both intraspecies and interspecies variability to the toxicity of this chemical in lieu of specific data, and 10 for extrapolation of a subchronic effect level to its chronic equivalent.

MF = 1

<<< Ethylbenzene >>>

___I.A.4. ADDITIONAL COMMENTS (ORAL RfD)

None.

___I.A.5. CONFIDENCE IN THE ORAL RfD

Study: Low
Data Base: Low
RfD: Low

Confidence in the chosen study is low because rats of only one sex were tested and the experiment was not of chronic duration. Confidence in the supporting data base is low because other oral toxicity data were not found. Low confidence in the RfD follows.

<<< Ethylbenzene >>>

___I.A.6. EPA DOCUMENTATION AND REVIEW OF THE ORAL RfD

U.S. EPA. 1980. Ambient Water Quality Criteria for Ethylbenzene. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Water Regulations and Standards, Washington, DC. EPA 440/5-80-048. NTIS PB 81-117590.

U.S. EPA. 1985. Drinking Water Criteria Document for Ethylbenzene. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Drinking Water, Washington, DC. (Public review draft)

U.S. EPA. 1985. Health Effects Assessment for Ethylbenzene. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Emergency and Remedial Response, Washington, DC. ECAO-CIN-H008.

The 1980 Ambient Water Quality Criteria Document for Ethylbenzene received extensive Agency and public review.

The 1985 Drinking Water Criteria Document for Ethylbenzene and the 1985 Health Effects Assessment for Ethylbenzene received extensive Agency review with the help of selected outside scientists.

Agency RfD Work Group Review: 05/20/85

Verification Date: 05/20/85

___I.A.7. EPA CONTACTS (ORAL RfD)

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------<<< Ethylbenzene >>>------

__I.B. REFERENCE DOSE FOR CHRONIC INHALATION EXPOSURE (RfDi)

Not available at this time

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_II. CARCINOGENICITY ASSESSMENT FOR LIFETIME EXPOSURE

Substance Name -- Ethylbenzene
CASRN -- 100-41-4
Last Revised -- 09/07/88

Section II provides information on three aspects of the carcinogenic risk assessment for the agent in question; the U.S. EPA classification, and quantitative estimates of risk from oral exposure and from inhalation exposure. The classification reflects a weight-of-evidence judgment of the likelihood that the agent is a human carcinogen. The quantitative risk estimates are presented in three ways. The slope factor is the result of application of a low-dose extrapolation procedure and is presented as the risk per mg/kg/day. The unit risk is the quantitative estimate in terms of either risk per ug/L drinking water or risk per ug/cu.m air breathed. The third form in which risk is presented is a drinking water or air concentration providing cancer risks of 1 in 10,000, 1 in 100,000 or 1 in 1,000,000. Background Document 2 (Service Code 5) provides details on the rationale and methods used to derive the carcinogenicity values found in IRIS. Users are referred to Section I for information on long-term toxic effects other than carcinogenicity.

<<< Ethylbenzene >>>

__II.A. EVIDENCE FOR CLASSIFICATION AS TO HUMAN CARCINOGENICITY

___II.A.1. WEIGHT-OF-EVIDENCE CLASSIFICATION

Classification -- D; not classifiable as to human carcinogenicity.

Basis -- nonclassifiable due to lack of animal bioassays and human studies.

___II.A.2. HUMAN CARCINOGENICITY DATA

None.

___II.A.3. ANIMAL CARCINOGENICITY DATA

None. NTP has plans to initiate bioassay. Metabolism and excretion studies at 3.5, 35 and 350 mg/kg are to be conducted as well.

<<< Ethylbenzene >>>

___II.A.4. SUPPORTING DATA FOR CARCINOGENICITY

The metabolic pathways for humans and rodents are different (Engstrom et al., 1984). Major metabolites in humans, mandelic acid and phenylglyoxylic acid, are minor metabolites in rats and rabbits (Kiese and Lenk, 1974). The major animal metabolites were not detected in the urine of exposed workers (Engstrom et al., 1984).

Ethylbenzene at 0.4 mg/plate was not mutagenic for Salmonella strains TA98, TA1535, TA1537 and TA1538 with or without Aroclor 1254 induced rat liver homogenates (S9) (Nestmann et al., 1980). Ethylbenzene was shown to increase the mean number of sister chromatid exchanges in human whole blood lymphocyte culture at the highest dose examined without any metabolic activation system (Norppa and Vainio, 1983).

Dean et al. (1985) used a battery of short-term tests including bacterial mutation assays, mitotic gene conversion in Saccharomyces cerevisiae JD1 in the presence and absence of S9 and chromosomal damage in a cultured rat liver cell line. Ethylbenzene was not mutagenic in the range of concentrations tested (0.2, 2, 20, 50 and 200 ug/plate) for S. typhimurium TA98, TA100, TA1535, TA1537 and TA1538 or for Escherichia coli WP2 and WP2uvrA. Ethylbenzene also showed no response in the S. cerevisiae JD1 gene conversion assay. In contrast, ethylbenzene hydroperoxide showed positive responses with E. coli WP2 at 200 ug/plate in the presence of S9 and an equally significant response with the gene conversion system of yeast.

__II.B. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM ORAL EXPOSURE

Not available.

__II.C. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM INHALATION EXPOSURE

Not available.

__II.D. EPA DOCUMENTATION, REVIEW, AND CONTACTS (CARCINOGENICITY ASSESSMENT) <<< Ethylbenzene >>>

___II.D.1. EPA DOCUMENTATION

U.S. EPA. 1980. Ambient Water Quality Criteria Document for Ethylbenzene. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Water Regulations and Standards, Washington, DC. EPA 440/5-80-048. NTIS PB 81-117590.

U.S. EPA. 1984. Health Effects Assessment for Ethylbenzene. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Emergency and Remedial Response, Washington, DC. EPA/540/1-86/008.

U.S. EPA. 1987. Drinking Water Criteria Document for Ethylbenzene. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Drinking Water, Washington, DC.

___II.D.2. REVIEW (CARCINOGENICITY ASSESSMENT)

The Ambient Water Quality Criteria Document and the Health Assessment Document have received Agency and external review. The Drinking Water Criteria Document has been extensively reviewed.

Agency Work Group Review: 10/07/87

Verification Date: 10/07/87

___II.D.3. U.S. EPA CONTACTS (CARCINOGENICITY ASSESSMENT)

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_III. HEALTH HAZARD ASSESSMENTS FOR VARIED EXPOSURE DURATIONS

Substance Name -- Ethylbenzene
CASRN -- 100-41-4
Last Revised -- 03/01/88

__III.A. DRINKING WATER HEALTH ADVISORIES

The Office of Drinking Water provides Drinking Water Health Advisories (HAs) as technical guidance for the protection of public health. HAs are not enforceable Federal standards. HAs are concentrations of a substance in drinking water estimated to have negligible deleterious effects in humans, when ingested, for a specified period of time. Exposure to the substance from other media is considered only in the derivation of the lifetime HA. Given the absence of chemical-specific data, the assumed fraction of total intake from drinking water is 10% for inorganic contaminants and 20% for organic contaminants. The lifetime HA is calculated from the Drinking Water Equivalent Level (DWEL) which, in turn, is based on the Oral Chronic Reference Dose. Lifetime HAs are not derived for compounds which are potentially carcinogenic for humans because of the difference in assumptions concerning toxic threshold for carcinogenic and noncarcinogenic effects. A more detailed description of the assumptions and methods used in the derivation of HAs is provided in Background Document 3 in Service Code 5.

<<< Ethylbenzene >>>

___III.A.1. ONE-DAY HEALTH ADVISORY FOR A CHILD

One-day HA -- 3.2E+1 mg/L

NOAEL -- 31.8 mg/kg/day
UF -- 10 (allows for intrahuman variability with the use of a NOAEL from a human study)
Assumptions -- 1 L/day water consumption for a 10-kg child

Principal Study -- Bardodej and Bardodejova, 1970

No adverse health effects were observed in human volunteers exposed to ethylbenzene by inhalation at a concentration of 100 ppm (435 mg/cu.m) for 8 hours. Based on the conditions of exposure and an assumed absorption factor of 64%, this is equivalent to a NOAEL of 31.8 mg/kg/day.

___III.A.2. TEN-DAY HEALTH ADVISORY FOR A CHILD

Appropriate data for calculating a Ten-day HA are not available. Therefore, the Ten-day HA has been calculated from the One-day HA by dividing the One-day HA of 32 mg/L by 10. The Ten-day HA is therefore 3.2 mg/L.

<<< Ethylbenzene >>>

___III.A.3. LONGER-TERM HEALTH ADVISORY FOR A CHILD

Appropriate data for calculating a Longer-term HA are not available. It is recommended that the modified DWEL (adjusted for a 10-kg child) of 0.97 mg/L (rounded to 1 mg/L) be used as the Longer-term HA.

___III.A.4. LONGER-TERM HEALTH ADVISORY FOR AN ADULT

Appropriate data for calculating a Longer-term HA are not available. It is recommended that the DWEL of 3.4 mg/L be used as the Longer-term HA for the 70-kg adult.

___III.A.5. DRINKING WATER EQUIVALENT LEVEL / LIFETIME HEALTH ADVISORY

DWEL -- 3.4E+0 mg/L

Assumptions -- 2 L/day water consumption for a 70-kg adult

RfD Verification Date = 05/20/85 (see Section I.A. of this file)

Lifetime HA -- 6.8E-1 mg/L

Assumptions -- 20% exposure by drinking water

Principal Study -- Wolf et al., 1956 (This study was used in the derivation of the chronic oral RfD; see Section I.A.2.)

<<< Ethylbenzene >>>

___III.A.6. ORGANOLEPTIC PROPERTIES

Taste perception threshold (water) -- 0.029 mg/L.

Odor perception threshold (water) -- 0.029 mg/L.

Odor perception threshold (air) -- 0.062 mg/L.

___III.A.7. ANALYTICAL METHODS FOR DETECTION IN DRINKING WATER

Analysis of ethylbenzene is by a purge-and-trap gas chromatographic procedure used for the detection of volatile organic compounds in water. Confirmatory analysis is by mass spectrometry.

___III.A.8. WATER TREATMENT

Ethylbenzene is most effectively removed from water by air stripping. Adsorption on activated carbon is at least partially effective in the removal of ethylbenzene from solution. Conventional treatment processes may also be effective.

<<< Ethylbenzene >>>

___III.A.9. DOCUMENTATION AND REVIEW OF HAs

U.S. EPA. 1985. Final Draft of the Drinking Water Criteria Document on Ethylbenzene. Office of Drinking Water, Washington, DC.

EPA review of HAs in 1985.

Public review of HAs following notification of availability in October, 1985.

Scientific Advisory Panel review of HAs in January, 1986.

Preparation date of this IRIS summary -- 06/24/87

___III.A.10. EPA CONTACTS

Charles O. Abernathy / ODW -- (202)382-5374 / FTS 382-5374

Edward V. Ohanian / ODW -- (202)382-7571 / FTS 382-7571

------<<< Ethylbenzene >>>------

__III.B. OTHER ASSESSMENTS

Content to be determined

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_IV. U.S. EPA REGULATORY ACTIONS

Substance Name -- Ethylbenzene
CASRN -- 100-41-4
Last Revised -- 03/01/88

EPA risk assessments may be updated as new data are published and as assessment methodologies evolve. Regulatory actions are frequently not updated at the same time. Compare the dates for the regulatory actions in this section with the verification dates for the risk assessments in sections I and II, as this may explain inconsistencies. Also note that some regulatory actions consider factors not related to health risk, such as technical or economic feasibility. Such considerations are indicated for each action. In addition, not all of the regulatory actions listed in this section involve enforceable federal standards. Please direct any questions you may have concerning these regulatory actions to the U.S. EPA contact listed for that particular action. Users are strongly urged to read the background information on each regulatory action in Background Document 4 in Service Code 5.

__IV.A. CLEAN AIR ACT (CAA)

No data available

------<<< Ethylbenzene >>>------

__IV.B. SAFE DRINKING WATER ACT (SDWA)

___IV.B.1. MAXIMUM CONTAMINANT LEVEL GOAL (MCLG) for Drinking Water

Value (status) -- 0.68 mg/L (Proposed, 1985)

Considers technological or economic feasibility? -- NO

Discussion -- An MCLG of 0.68 mg/L for ethylbenzene is proposed based upon a provisional DWEL of 3.4 mg/L and an assumed drinking water contribution of 20%. A DWEL of 3.4 mg/L was calculated from a NOAEL of 136 mg/kg/day for histopathological changes (not specified) in rats (6-month oral study) with an uncertainty factor of 1000, conversion factor of 5/7 and consumption of 2 L of water/day.

Reference -- 50 FR 46936 Part IV (11/13/85)

EPA Contact -- Charles Abernathy / Criteria and Standards Division, ODW / (202)382-7571 / FTS 382-7571; or Drinking Water Hotline / (800)426-4791

------<<< Ethylbenzene >>>------

__IV.C. CLEAN WATER ACT (CWA)

___IV.C.1. AMBIENT WATER QUALITY CRITERIA, Human Health

Water and Fish Consumption: 1.4 mg/L

Fish Consumption Only: 3.28 mg/L

Considers technological or economic feasibility? -- NO

Discussion -- The WQC of 1.4 mg/L is based on consumption of contaminated aquatic organisms and water. A WQC of 3.28 mg/L has also been established based on consumption of contaminated aquatic organisms alone.

Reference -- 45 FR 79318 (11/28/80)

EPA Contact -- Criteria and Standards Division / OWRS / (202)475-7315 / FTS 475-7315

<<< Ethylbenzene >>>

__IV.C.2. AMBIENT WATER QUALITY CRITERIA, Aquatic Organisms

Freshwater:

Acute -- 32,000 ug/L (LEL)
Chronic -- None

Marine:

Acute -- 430 ug/L (LEL)
Chronic -- None

Considers technological or economic feasibility? -- NO

Discussion -- Water quality criteria for the protection of aquatic life are derived from a minimum data base of acute and chronic tests on a variety of aquatic organisms. The "(LEL)" after the value indicates that the minimum data were not available and the concentration given is not a criteria value but the lowest effect level found in the literature.

Reference -- 45 FR 79318 (11/28/80)

EPA Contact -- Criteria and Standards Division / OWRS / (202)475-7315 / FTS 475-7315

------<<< Ethylbenzene >>>------

__IV.D. FEDERAL INSECTICIDE, FUNGICIDE, AND RODENTICIDE ACT (FIFRA)

No data available

------<<< Ethylbenzene >>>------

__IV.E. TOXIC SUBSTANCES CONTROL ACT (TSCA)

No data available

------<<< Ethylbenzene >>>------

__IV.F. RESOURCE CONSERVATION AND RECOVERY ACT (RCRA)

___IV.F.1. RCRA APPENDIX IX, for Ground Water Monitoring

Status -- Listed

Reference -- 52 FR 25942 (07/09/87)

EPA Contact -- Jerry Garman / OSW / (202)382-4658 / FTS 382-4658

------<<< Ethylbenzene >>>------

__IV.G. SUPERFUND (CERCLA)

___IV.G.1. REPORTABLE QUANTITY (RQ) for Release into the Environment

Value (status) -- 1000 pounds (Final, 1985)

Considers technological or economic feasibility? -- NO

Discussion -- The final RQ is based on aquatic toxicity, as established under Section 311(b)(4) of the Clean Water Act (40 CFR 117.3), and ignitability. Available data indicate that the aquatic 96-Hour Median Threshold Limit for ethylbenzene is between 10 and 100 ppm. The closed-cup flash point is less than 100F and the boiling point is >100F.

Reference -- 50 FR 13456 (04/04/85)

EPA Contact -- RCRA/Superfund Hotline
(800)424-9346 / (202)382-3000 / FTS 382-3000

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_V. SUPPLEMENTARY DATA

Substance Name -- Ethylbenzene
CASRN -- 100-41-4

Not available at this time

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_VI. BIBLIOGRAPHY

Substance Name -- Ethylbenzene
CASRN -- 100-41-4
Last Revised -- 08/01/89

__VI.A. ORAL RfD REFERENCES

U.S. EPA. 1980. Ambient Water Quality Criteria Document for Ethylbenzene. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Water Regulations and Standards, Washington, DC. EPA 440/5-80-048. NTIS PB 81-117590.

U.S. EPA. 1985. Drinking Water Criteria Document for Ethylbenzene. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Drinking Water, Washington, DC. (Final draft)

U.S. EPA. 1984. Health Effects Assessment for Ethylbenzene. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Emergency and Remedial Response, Washington, DC.

Wolf, M.A., V.K. Rowe, D.D. McCollister, R.L. Hollingsworth and F. Oyen. 1956. Toxicological studies of certain alkylated benzenes and benzene. Arch. Ind. Health. 14: 387-398.

------<<< Ethylbenzene >>>------

__VI.B. INHALATION RfD REFERENCES

None

------<<< Ethylbenzene >>>------

__VI.C. CARCINOGENICITY ASSESSMENT REFERENCES

Dean, B.J., T.M. Brooks, G. Hodson-Walker and D.H. Hutson. 1985. Genetic toxicology testing of 41 industrial chemicals. Mutat. Res. 153: 57-77.

Engstrom, K., V. Riihimaki and A. Laine. 1984. Urinary disposition of ethylbenzene and m-xylene in man following separate and combined exposure. Int. Arch. Occup. Environ. Health. 54: 355-363.

Kiese, M. and W. Lenk. 1974. Hydroxyacetophenones: Urinary metabolites of ethylbenzene and acetophenone in the rabbit. Xenobiotica. 4(6): 337-343.

Nestmann, E.R., E.G-H. Lee, T.I. Matula, G.R. Douglas and J.C. Mueller. 1980. Mutagenicity of constituents identified in pulp and paper mill effluent using the Salmonella/mammalian-microsome assay. Mutat. Res. 79: 203-212.

Norppa, H. and H. Vainio. 1983. Induction of sister-chromatid exchanges by styrene analogues in cultured human lymphocytes. Mutat. Res. 116: 379-387.

U.S. EPA. 1980. Ambient Water Quality Criteria Document for Ethylbenzene. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Water Regulations and Standards, Washington, DC. EPA 440/5-80-048. NTIS PB 81-117590.

U.S. EPA. 1984. Health Effects Assessment for Ethylbenzene. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Emergency and Remedial Response, Washington, DC.

U.S. EPA. 1987. Drinking Water Criteria Document for Ethylbenzene. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Drinking Water, Washington, DC. (Final report)

------<<< Ethylbenzene >>>------

__VI.D. DRINKING WATER HA REFERENCES

Bardodej, Z. and E. Bardodejova. 1970. Biotransformation of ethylbenzene, styrene and alpha-methylstyrene in man. Am. Ind. Hyg. Assoc. J. 31(2): 206-209.

Wolf, M.A., V.K. Rowe, D.D. McCollister, R.L. Hollingsworth and F. Oyen. 1956. Toxicological studies of certain alkylated benzenes and benzene. Arch. Ind. Health. 14: 387-398.

U.S. EPA. 1985. Drinking Water Criteria Document on Ethylbenzene. Office of Drinking Water, Washington, DC. (Final draft)

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SYNONYMS

100-41-4
AETHYLBENZOL
BENZENE, ETHYL
EB
ETHYLBENZEEN
Ethylbenzene

ETHYLBENZOL
ETILBENZENE
ETYLOBENZEN
NCI-C56393
PHENYLETHANE
UN 1175

C-8 (e) TETRAHYDROFURAN

C-8 (e) TETRAHYDROFURAN

The attached reference, "Provisional RfD for Tetrahydrofuran" is provided as technical background information due to lack of more detailed toxicological data available in the literature. As discussed in the text, confidence in the provisional RfD is low, as indicated by an uncertainty factor of 10,000 applied to the no observed-adverse health affects level (NOAEL) of 22 mg/kg/day (Hurst 1990). The uncertainty factor of 10,000 included evaluation of four elements of applicability or utility, each which may result in overestimating risk as well as underestimating risk. In each instance, the EPA Environmental Criteria and Assessment Office (ECAO) applied a high-end (i.e., conservative) uncertainty factor to each element, assuming each element would serve to underestimate risk; this will tend to provide a very conservative basis for estimation of RfD. In turn, the ECAO-supplied oral RfD likely overestimates tetrahydrofuran human toxicity. The uncertainty factor of 10,000 applied to tetrahydrofuran was found to be one or more orders of magnitude greater than for uncertainty factors applied to the other selected indicator compounds. Due to the unusually higher upper-end uncertainty factor applied to tetrahydrofuran, it is likely that the toxicity of tetrahydrofuran is no greater than for other selected indicator compounds.

6185/816

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
OFFICE OF RESEARCH AND DEVELOPMENT
ENVIRONMENTAL CRITERIA AND ASSESSMENT OFFICE
CINCINNATI, OHIO 45268

May 3, 1990

SUBJECT: Provisional RfD for Tetrahydrofuran (THF)

FROM: Pei-Fung Hurst
Biologist
Chemical Mixtures Assessment Branch

TO: Rodger Duart
U.S EPA
Region I

THRU: W. Bruce Peirano
Acting Chief
Chemical Mixture Assessment Branch

This memo is a draft response to your request for an oral assessment of the toxicity of tetrahydrofuran (THF) for the Mottolo NPL site. Although an oral RfD for THF was prepared and presented to the RfD Work Group on 01/28/87, it was not verified and was placed under review until a complete translation of the critical study (Katahira, 1982), published in Japanese, could be obtained. (An inhalation RfD for THF, based upon this same study, has been verified on 1/19/90.) Consequentially, ECAO has obtained a full translation of the Katahira (1982) study and based an interim oral RfD for THF of 0.002 mg/kg/day upon this data. Below is a summary of the Katahira (1982) study and oral RfD computations.

Male SD rats (11-12/group) were exposed to 0, 100, 200, 1000 or 5000 ppm (0, 295, 590,2449, or 14,744 mg/m^3) 4 hr/day, 5 day/week for 12 weeks. Rats exposed to 100 or 200 ppm had no effects other than redness about the eyes and nose. Increased levels of SGOT, indicative of liver damage, were observed in the rats exposed to 1000 ppm. Rats exposed to 5000 ppm had marked local irritation (edema or opacity of the cornea, salivation, discharge or bleeding from the nose), morphologically defined damage to the respiratory mucosa, significant alterations in blood counts and blood sugar, increased levels of SGOT, SGPT, and bilirubin and CNS effects (clonic muscle spasms, coma, cataleptoid posture). The rise in SGOT levels was dose related. Although a statistically significant increase in SGOT levels in rats exposed to 200 ppm is indicated in a table presented in the publication, the author only notes that increased serum enzyme changes were observed in the two highest exposure levels. There were no changes in relative or absolute organ weights and no histopathological alterations in the brain, lungs, liver, spleen, kidneys or femur were detected in the exposed animals. Thus, the NOAEL for liver effects is 200 ppm, which is equivalent to an oral dose of 22 mg/kg/day. Application of an uncertainty factor of 10,000 (10 for use of a subchronic study; 10 for interspecies extrapolation. 10 for intraspecies variability, and 10 to account for the limited database) to the NOAEL yields an oral RfD of 0.002 mg/kg/day.

Conversion factors: 4 hr/24 hr, 5 day/7 day, 0.223 mg/m^3 rat inhalation rate, 0.35 kg rat body weight, 0.5 absorption factor (i.e. 590 mg/m^3 x 4 hr/24 hr x 5 day/7 day x 0.223 m^3/day x 1/0.35 kg x 0.5 = 22.4 mg/kg/day.

Although, this study did not find definitive evidence of liver damage, other studies have shown that the liver is a target organ. Katahira (1982) cites that other studies have reported liver damage in cats and rats following inhalation, intravenous, or intramedullary injection (Lehmann and Flury, 1943; Okhumra, 1958; Jochmann, 1961).

Liver effects (centrilobular cytomegaly) were observed in mice exposed to 5000 ppm THF 6 hr/day, 5 day/week for 13 weeks. Liver effects were not observed in rats in this study; however, acanthosis and supportive inflammation of the forestomach was observed in rats exposed to 5000 ppm (Grumbien, 1988)

Critical Studies:

Katahira, T. 1982. [Experimental studies on the toxicity of tetrahydrofuran]. Osaka Shiritsu Daugaku Igaku Zasshi 31;221-239. (Japanese)

Grumbein, S. 1988. 13-Week subchronic toxicity test by inhalation of tetrahydrofuran in Fisher 344 rats and B6C3F1 mice. Pathology Working Group Chairperson's Report. Submitted to National Toxicology Program, Research Triangle Park, NC.

Please note that the number derived is an interim number and ECAO is seeking further review of this assessment. We will forward any additional information to you as soon as it is available. Should you desire any additional information, do not hesitate to call me at FTS 684-7300

cc: C. DeRosa (ECAO-Cin)
S. Levinson (Region I)
B. Means (OS-230)
T. O'Bryan (OS-230)
S. Sokol (Balson Environmental Consulting)

C-8 (f) 1,1,1-TRICHLOROETHANE

The attached Integrated Risk Information System (IRIS) printout (March 1990) is provided as a technical summary.

1,1,1-Trichloroethane; CASRN 71-55-6 (06/01/89)

Health risk assessment information on a chemical is included in IRIS only after a comprehensive review of chronic toxicity data by work groups composed of U.S. EPA scientists from several Program Offices. The summaries presented in Sections I and II represent a consensus reached in the review process. The other sections contain U.S. EPA information which is specific to a particular EPA program and has been subject to review procedures prescribed by that Program Office. The regulatory actions in Section IV may not be based on the most current risk assessment, or may be based on a current, but unreviewed, risk assessment, and may take into account factors other than health effects (e.g., treatment technology). When considering the use of regulatory action data for a particular situation, note the date of the regulatory action, the date of the most recent risk assessment relating to that action, and whether technological factors were considered. Background information and explanations of the methods used to derive the values given in IRIS are provided in the five Background Documents in Service Code 5, which correspond to Sections I through V of the chemical files.

STATUS OF DATA FOR 1,1,1-Trichloroethane

File On-Line 03/31/87

Category (section)	Status	Last Revised
Oral RfD Assessment (I.A.)	on-line	06/30/88
Inhalation RfD Assessment (I.B.)	no data	
Carcinogenicity Assessment (II.)	on-line	06/01/89
Drinking Water Health Advisories (III.A.)	no data	
U.S. EPA Regulatory Actions (IV.)	on-line	03/01/88

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_I. CHRONIC HEALTH HAZARD ASSESSMENT FOR NONCARCINOGENIC EFFECTS

Substance Name -- 1,1,1-Trichloroethane
CASRN -- 71-55-6
Last Revised -- 06/30/88

The Reference Dose (RfD) is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis, but may not exist for other toxic effects such as carcinogenicity. In general, the RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Please refer to Background Document 1 in Service Code 5 for an elaboration of these concepts. RfDs can also be derived for the noncarcinogenic health effects of compounds which are also carcinogens. Therefore, it is essential to refer to other sources of information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file when a review of that evaluation is completed.

<<< 1,1,1-Trichloroethane >>>

__I.A. REFERENCE DOSE FOR CHRONIC ORAL EXPOSURE (RfDo)

___I.A.1. ORAL RfD SUMMARY

Critical Effect	Experimental Doses*	UF	MF	RfD
No adverse effects Guinea Pig 6-Month Inhalation Study Torkelson et al., 1958	NOAEL: 500 ppm (air) (2730 mg/cu.m) converted to 90/mg/kg/day	1000	1	9E-2 mg/kg/day
Slight growth retardation Guinea Pig 2-3 Month Inhalation Study Adams et al., 1950	LOAEL: 650 ppm (air) (3550 mg/cu.m) (converted to 120 mg/kg/day)			

*Dose Conversion Factors & Assumptions: dose (mg/cu.m) x 7 hours/24 hours x 5 days x (0.3) x (0.23 cu.m/day/0.43 kg) where: 0.3 is the assumed inhalation retention factor, and 0.23 cu.m/day /0.43 kg are the assumed ventilation rate and body weight of the guinea pig, respectively.

<<< 1,1,1-Trichloroethane >>>

___I.A.2. PRINCIPAL AND SUPPORTING STUDIES (ORAL RfD)

Torkelson, T.R., F. Oyen, D.D. McCollister and V.K. Rowe. 1958. Toxicity of 1,1,1-trichloroethane as determined on laboratory animals and human subjects. Am. Ind. Hyg. Assoc. J. 19: 353-362.

Adams, E.M., H.C. Spencer, V.K. Rowe and D.D. Irish. 1950. Vapor toxicity of 1,1,1-trichloroethane (methyl chloroform) determined by experiments on laboratory animals. Arch. Ind. Hyg. Occup. Med. 1: 225-236.

Torkelson et al. (1958) exposed groups of rats, rabbits, guinea pigs and monkeys to 1,1,1-trichloroethane vapor at concentrations of 500, 1000, 2000, or 10,000 ppm. From these studies, it was determined that the female guinea pig was the most sensitive species of those tested. At 500 ppm, groups of eight male and eight female guinea pigs showed no evidence of adverse effects compared with unexposed and air-exposed controls after exposure for 7 hours/day, 5 days/week for 6 months. Groups of five female guinea pigs exposed to 1000 ppm 1,1,1-trichloroethane vapor 3 hours/day, 5 days/week for 3 months had fatty changes in the liver and statistically significant increased liver weights. Thus, this study defined a NOAEL of 500 ppm (2730 mg/cu.m) in guinea pigs.

Adams et al. (1950) subjected groups of 6-10 male and female guinea pigs to 650 ppm 1,1,1-trichloroethane vapor 7 hours/day, 5 days week for 2 to 3 months. These animals exhibited a slight depression in weight gain compared with both air-exposed and unexposed controls, thereby establishing a LOAEL of 650 ppm (3550 mg/cu.m) in guinea pigs.

<<< 1,1,1-Trichloroethane >>>

___I.A.3. UNCERTAINTY AND MODIFYING FACTORS (ORAL RfD)

UF = 1000. Factors of 10 each were employed for use of a subchronic assay, for extrapolation from animal data, and for protection of sensitive human subpopulations.

MF = 1

___I.A.4. ADDITIONAL COMMENTS (ORAL RfD)

The 1,1,1-trichloroethane samples used by Torkelson et al. (1958) were found to be 94-97% pure while the samples used in the Adams et al. (1950) study had a purity of greater than or equal to 99%.

The effects of 1,1,1-trichloroethane vapor have been investigated in mice (Quast et al., 1984; McNutt et al., 1975), rats (Quast et al., 1978), and rabbits and dogs (Pendergast et al., 1967). The only chronic oral exposure study was conducted by NCI (1977) in rats. The observations from these studies and from Torkelson et al. (1958) and Adams et al. (1950) are somewhat inconsistent, thus making conclusions difficult as to the dose levels of 1,1,1-trichloroethane that result in adverse effects. For example, exposure to 650 ppm in the Adams et al. (1950) inhalation study was associated with slight growth retardation in guinea pigs. Further review of this study indicates that 1500 ppm exposure also caused slight growth retardation without causing any organ-specific adverse effects following 1 to 3 months exposure. These observations are in contrast with those of Torkelson et al. (1958), who observed adverse effects in the liver and lungs of guinea pigs exposed to 1000 ppm for 90 days.

Results and technical evaluation of recent inhalation studies in mice (Quast et al., 1984) and rats conducted by Dow Chemical when published may be of greater value for the overall RfD consideration for 1,1,1-trichloroethane.

<<< 1,1,1-Trichloroethane >>>

___I.A.5. CONFIDENCE IN THE ORAL RfD

Study: Low
Data Base: Medium
RfD: Medium

Although both the Adams et al. (1950) and Torkelson et al. (1958) studies used both sexes of several species, the number of animals at each dose level was limited, the length of exposure varied with different dose levels and few toxic endpoints were examined. Confidence in these studies is thus considered low. The data base is fairly comprehensive; however, results from these studies are somewhat inconsistent and some of the more recent studies have yet to be critically evaluated. Confidence in the data base is, therefore, rated medium. Confidence in the RfD can be considered medium to low.

___I.A.6. EPA DOCUMENTATION AND REVIEW OF THE ORAL RfD

The only U.S. EPA documentation at present is on IRIS.

Agency RfD Work Group Review: 05/31/85, 07/08/85, 07/22/85, 05/15/86

Verification Date: 05/15/86

___I.A.7. EPA CONTACTS (ORAL RfD)

Yogendra Patel / ODW -- (202)382-7585 / FTS 382-7585

Michael L. Dourson / ORD -- (513)569-7544 / FTS 684-7544

------<<< 1,1,1-Trichloroethane >>>------

__I.B. REFERENCE DOSE FOR CHRONIC INHALATION EXPOSURE (RfDi)

Not available at this time

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_II. CARCINOGENICITY ASSESSMENT FOR LIFETIME EXPOSURE

Substance Name -- 1,1,1-Trichloroethane
CASRN -- 71-55-6
Last Revised -- 06/01/89

Section II provides information on three aspects of the carcinogenic risk assessment for the agent in question; the U.S. EPA classification, and quantitative estimates of risk from oral exposure and from inhalation exposure. The classification reflects a weight-of-evidence judgment of the likelihood that the agent is a human carcinogen. The quantitative risk estimates are presented in three ways. The slope factor is the result of application of a low-dose extrapolation procedure and is presented as the risk per mg/kg/day. The unit risk is the quantitative estimate in terms of either risk per ug/L drinking water or risk per ug/cu.m air breathed. The third form in which risk is presented is a drinking water or air concentration providing cancer risks of 1 in 10,000, 1 in 100,000 or 1 in 1,000,000. Background Document 2 (Service Code 5) provides details on the rationale and methods used to derive the carcinogenicity values found in IRIS. Users are referred to Section I for information on long-term toxic effects other than carcinogenicity.

<<< 1,1,1-Trichloroethane >>>

__II.A. EVIDENCE FOR CLASSIFICATION AS TO HUMAN CARCINOGENICITY

___II.A.1. WEIGHT-OF-EVIDENCE CLASSIFICATION

Classification -- D; not classifiable as to human carcinogenicity.

Basis -- There are no reported human data and animal studies (one lifetime gavage, one intermediate-term inhalation) have not demonstrated carcinogenicity. Technical grade 1,1,1-trichloroethane has been shown to be weakly mutagenic, although the contaminant, 1,4-dioxane, a known animal carcinogen, may be responsible for this response.

___II.A.2. HUMAN CARCINOGENICITY DATA

None.

<<< 1,1,1-Trichloroethane >>>

___II.A.3. ANIMAL CARCINOGENICITY DATA

Inadequate. The NCI (1977) treated 50 male and 50 female Osborne-Mendel rats with 750 or 1500 mg/kg technical-grade 1,1,1-trichloroethane 5 times/week for 78 weeks by gavage. The rats were observed for an additional 32 weeks. Twenty rats of each sex served as untreated controls. Low survival of both male and female treated rats (3%) may have precluded significant development of tumors late in life. Although a variety of neoplasms was observed in both treated and matched control rats, they were common to aged rats and were not significantly related to dosage. Similar results were obtained when the NCI (1977) treated B6C3F1 hybrid mice with the time-weighted average doses of 2807 or 5615 mg/kg 1,1,1-trichloroethane by gavage 5 days/week for 78 weeks. The mice were observed for an additional 12 weeks. The control and treated groups had 20 and 50 animals of each sex, respectively. Only 25 to 45% of those treated survived until the time of terminal sacrifice. A variety of neoplasms were observed in treated groups but with an incidence not statistically different from matched controls.

Quast et al. (1978) exposed 96 Sprague-Dawley rats of both sexes to 875 or 1750 ppm 1,1,1-trichloroethane vapor for 6 hours/day, 5 days/week for 12 months, followed by an additional 19-month observation period. The only significant sign of toxicity was an increased incidence of focal hepatocellular alterations in female rats at the highest dosage. It was not evident that a maximum tolerated dose (MTD) was used nor was a range-finding study conducted. No significant dose-related neoplasms were reported, but these dose levels were below those used in the NCI study.

<<< 1,1,1-Trichloroethane >>>

___II.A.4. SUPPORTING DATA FOR CARCINOGENICITY

Mutagenicity testing of 1,1,1-trichloroethane has produced positive results in S. typhimurium strain TA100 (Simmon et al., 1977; Fishbein, 1979; Snow et al., 1979) as well as some negative results (Henschler et al., 1977; Taylor, 1978).

It was mutagenic for S. typhimurium strain TA1535 both with exogenous metabolic activation (Farber, 1977) and without activation (Nestmann et al., 1980). 1,1,1-Trichloroethane did not result in gene conversion or mitotic recombination in Saccharomyces cerevisiae (Farber, 1977; Simmon et al., 1977) nor was it positive in a host-mediated forward mutation assay using Schizosaccharomyces pombe in mice. The chemical also failed to produce chromosomal aberrations in the bone marrow of cats (Rampy et al., 1977), but responded positively in a cell transformation test with rat embryo cells (Price et al., 1978).

An isomer, 1,1,2-trichloroethane, is carcinogenic in mice, inducing liver cancer and pheochromocytomas in both sexes. Dichloroethanes, tetrachloroethanes and hexachloroethanes also produced liver cancer in mice and other types of neoplasms in rats.

It should be noted that 1,4-dioxane, a known animal carcinogen, is a contaminant of technical-grade 1,1,1-trichlorethane. It causes liver and nasal tumors in more than one strain of rats and hepatocellular carcinomas in mice.

___II.B. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM ORAL EXPOSURE

Not available.

__II.C. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM INHALATION EXPOSURE

Not available.

__II.D. EPA DOCUMENTATION, REVIEW, AND CONTACTS (CARCINOGENICITY ASSESSMENT) <<< 1,1,1-Trichloroethane >>>

___II.D.1. EPA DOCUMENTATION

U.S. EPA. 1984a. Health Effects Assessment for 1,1,1-Trichloroethane. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Emergency and Remedial Response, Washington, DC. ECAO-CIN-H005.

U.S. EPA. 1984b. Health Assessment Document for 1,1,1-Trichloroethane. Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Research Triangle Park, NC. EPA-600/8-82-003F.

Farber, H. 1977. Manager of Environmental Affairs, Dow Chemical letter to James Price, Chief of Air Quality Data Analysis, Texas Air Control Board, Austin, TX. Cited in NCI, 1977.

Fishbein, L. 1979. Potential halogenated industrial carcinogenic and mutagenic chemicals. II. Halogenated saturated hydrocarbons. Sci. Total Environ. 11: 163.

Henschler, D., E. Eder, T. Neudecker and M. Metzler. 1977. Carcinogenicity of trichloroethylene: Fact or artifact? Arch. Toxicol. 37: 233-236.

NCI (National Cancer Institute). 1977. Bioassay of 1,1,1-trichloroethane for possible carcinogenicity. Carcinog. Tech. Rep. Ser. No. 3, NCI-CG-TR-3.

Nestman, E.R., E.G.H. Lee, T.I. Matula, G.R. Douglas and J.C. Mueller. 1980. Mutagenicity of constituents identified in pulp and paper mill effluents using the Salmonella/mammalian-microsome assay. Mutat. Res. 79: 203-212.

Price, P.J., C.M. Hassett and J.I. Mansfield. 1978. Transforming activities of trichloroethylene and proposed industrial alternatives. In vitro. 14: 290-293.

Quast, J.F., B.K.J. Leong, L.W. Rampy and P.J. Gehring. 1978. Toxicologic and carcinogenic evaluation of a methylchloroform (1,1,1-trichloroethane) formulation by chronic inhalation in rats -- interim report after 24 months. Dow Chemical Co., Midland, MI.

Rampy, L.W., J.F. Quast, B.K.J. Leong and P.J. Gehring. 1977. Results of long-term inhalation toxicity studies on rats of 1,1,1-trichloroethane and perchloroethylene formulations. In: Proc. Int. Cong. Toxicol. Toronto.

Simmon, V.F., et al. 1977. Mutagenic activity of chemicals identified in drinking water. In: Progress in Genetic Toxicology, D. Scott et al., Ed. Elsevier/North Holland Biomedical Press, Amsterdam.

Snow, L.P., B.C. Nair and B.C. Castro. 1979. Mutagenic testing of 1,1,1-trichloroethane in Salmonella strains TA100 and TA98. Northrop Services, Inc., Research Triangle Park, NC.

Taylor, G. 1978. Personal communication. NIOSH, Morgantown, WV. Cited in U.S. EPA, 1984a.

<<< 1,1,1-Trichloroethane >>>

___II.D.2. REVIEW (CARCINOGENICITY ASSESSMENT)

The 1984 Health Effects Assessment for 1,1,1-Trichloroethane has received limited Agency review. The values in the 1984 Health Assessment Document for 1,1,1-Trichloroethane have received both Agency and public review.

Agency Work Group Review: 08/05/87

Verification Date: 08/05/87

___II.D.3. U.S. EPA CONTACTS (CARCINOGENICITY ASSESSMENT)

Charlingayya Hiremath / ORD -- (202)382-5898 / FTS 382-5898

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_III. HEALTH HAZARD ASSESSMENTS FOR VARIED EXPOSURE DURATIONS

Substance Name -- 1,1,1-Trichloroethane
CASRN -- 71-55-6

Not available at this time

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_IV. U.S. EPA REGULATORY ACTIONS

Substance Name -- 1,1,1-Trichloroethane
CASRN -- 71-55-6

Last Revised -- 03/01/88

EPA risk assessments may be updated as new data are published and as assessment methodologies evolve. Regulatory actions are frequently not updated at the same time. Compare the dates for the regulatory actions in this section with the verification dates for the risk assessments in sections I and II, as this may explain inconsistencies. Also note that some regulatory actions consider factors not related to health risk, such as technical or economic feasibility. Such considerations are indicated for each action. In addition, not all of the regulatory actions listed in this section involve enforceable federal standards. Please direct any questions you may have concerning these regulatory actions to the U.S. EPA contact listed for that particular action. Users are strongly urged to read the background information on each regulatory action in Background Document 4 in Service Code 5.

__IV.A. CLEAN AIR ACT (CAA)

No data available

------<<< 1,1,1-Trichloroethane >>>------

__IV.B. SAFE DRINKING WATER ACT (SDWA)

___IV.B.1. MAXIMUM CONTAMINANT LEVEL GOAL (MCLG) for Drinking Water

Value (status) -- 200 ug/L (Final, 1985)

Considers technological or economic feasibility? -- NO

Discussion -- An MCLG of 200 ug/L for 1,1,1-trichloroethane is proposed based upon a DWEL and an assumed drinking water contribution of 20%. A DWEL of 1.0 mg/L was calculated based on liver toxicity in mice (inhalation study).

Reference -- 50 FR 46880

EPA Contact -- Yogendra Patel, Criteria and Standards Division, ODW / (202)382-7571 / FTS 382-7571; or Drinking Water Hotline / (800)426-4791

<<< 1,1,1-Trichloroethane >>>

___IV.B.2. MAXIMUM CONTAMINANT LEVEL (MCL) for Drinking Water

Value (status) -- 200 ug/L (Final, 1987)

Considers technological or economic feasibility? -- NO

Discussion --

Reference -- 52 FR 25690

EPA Contact -- Yogendra Patel / Criteria and Standards Division, ODW /
(202)382-7571 / FTS 382-7571; or Drinking Water Hotline / (800)426-4791

------<<< 1,1,1-Trichloroethane >>>------

__IV.C. CLEAN WATER ACT (CWA)

___IV.C.1. AMBIENT WATER QUALITY CRITERIA, Human Health

Water and Fish Consumption -- 1.84E+4 ug/L

Fish Consumption Only -- 1.03E+6 ug/L

Considers technological or economic feasibility? -- NO

Discussion --

Reference -- 45 FR 79318 (11/28/80)

EPA Contact -- Criteria and Standards Division, OWRS
(202)475-7315 / FTS 475-7315

<<< 1,1,1-Trichloroethane >>>

___IV.C.2. AMBIENT WATER QUALITY CRITERIA, Aquatic Organisms

Freshwater:

Acute LEC -- None
Chronic LEC -- None

Marine:

Acute LEC -- 3.12E+4 ug/L
Chronic LEC -- None

Considers technological or economic feasibility? -- NO

Discussion -- The values that are indicated as "LEC" are not criteria, but are the lowest effect levels found in the literature. LECs are given when the minimum data required to derive water quality criteria are not available.

Reference -- 45 FR 79318 (11/28/80)

EPA Contact -- Criteria and Standards Division, OWRS
(202)475-7315 / FTS 475-7315

------<<< 1,1,1-Trichloroethane >>>------

__IV.D. FEDERAL INSECTICIDE, FUNGICIDE, AND RODENTICIDE ACT (FIFRA)

No data available

------<<< 1,1,1-Trichloroethane >>>------

__IV.E. TOXIC SUBSTANCES CONTROL ACT (TSCA)

No data available

------<<< 1,1,1-Trichloroethane >>>------

__IV.F. RESOURCE CONSERVATION AND RECOVERY ACT (RCRA)

___IV.F.1. RCRA APPENDIX IX, for Ground Water Monitoring

Status -- Listed

Reference -- 52 FR 25942 (07/09/87)

EPA Contact -- Jerry Garman / OSW / (202)382-4658 / FTS 382-4658

------<<< 1,1,1-Trichloroethane >>>------

__IV.G. SUPERFUND (CERCLA)

___IV.G.1. REPORTABLE QUANTITY (RQ) for Release into the Environment

Value (status) -- 1000 pounds (Final, 1985)

Considers technological or economic feasibility? -- NO

Discussion -- The final RQ is based on aquatic and chronic toxicity. Available data indicate a 96-hour Median Threshold Limit between 10 and 100 ppm, which corresponds to an RQ of 1000 pounds. RQ assignments based on chronic toxicity reflect two primary attributes, the minimum effect dose (MED) levels for chronic exposure (mg/day for 70-kg man) and the type of effect (teratogenicity, etc.). The composite score of these attributes for this substance is 6.0, corresponding to an RQ of 1000 pounds.

Reference -- 50 FR 13456 (04/04/85)

EPA Contact -- RCRA/Superfund Hotline
(800)424-9346 / (202)382-3000 / FTS 382-3000

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_V. SUPPLEMENTARY DATA

Substance Name -- 1,1,1-Trichloroethane
CASRN -- 71-55-6

Not available at this time

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_VI. BIBLIOGRAPHY

Substance Name -- 1,1,1-Trichloroethane
CASRN -- 71-55-6

Not available at this time

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SYNONYMS

71-55-6
AEROTHENE TT
CHLOROETENE
CHLOROETHENE
CHLOROETHENE NU
CHLOROFORM, METHYL-
CHLOROTHANE NU
CHLOROTHENE
CHLOROTHENE NU
CHLOROTHENE VG
CHLORTEN
ETHANE, 1,1,1-TRICHLORO-
INHIBISOL
METHYLCHLOROFORM
METHYLTRICHLOROMETHANE
NCI-C04626
RCRA WASTE NUMBER U226
STROBANE
alpha-T
1,1,1-TCE
1,1,1-TRICHLOORETHAAN
1,1,1-TRICHLORAETHAN
Trichloroethane, 1,1,1-

alpha-TRICHLOROETHANE
1,1,1-TRICLOROETANO
TRI-ETHANE
UN 2831

C-8 (g) TRICHLOROETHENE

The attached Integrated Risk Information System (IRIS) printout (March 1990) is provided as a technical summary.

Trichloroethylene; CASRN 79-01-6 (12/01/89)

Health risk assessment information on a chemical is included in IRIS only after a comprehensive review of chronic toxicity data by work groups composed of U.S. EPA scientists from several Program Offices. The summaries presented in Sections I and II represent a consensus reached in the review process. The other sections contain U.S. EPA information which is specific to a particular EPA program and has been subject to review procedures prescribed by that Program Office. The regulatory actions in Section IV may not be based on the most current risk assessment, or may be based on a current, but unreviewed, risk assessment, and may take into account factors other than health effects (e.g., treatment technology). When considering the use of regulatory action data for a particular situation, note the date of the regulatory action, the date of the most recent risk assessment relating to that action, and whether technological factors were considered. Background information and explanations of the methods used to derive the values given in IRIS are provided in the five Background Documents in Service Code 5, which correspond to Sections I through V of the chemical files.

STATUS OF DATA FOR Trichloroethylene

File On-Line 03/31/87

Category (section)	Status	Last Revised
Oral RfD Assessment (I.A.)	pending	
Inhalation RfD Assessment (I.B.)	pending	
Carcinogenicity Assessment (II.)	withdrawn	07/01/89
Drinking Water Health Advisories (III.A.)	no data	
U.S. EPA Regulatory Actions (IV.)	on-line	03/01/88

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_I. CHRONIC HEALTH HAZARD ASSESSMENT FOR NONCARCINOGENIC EFFECTS

Substance Name -- Trichloroethylene
CASRN -- 79-01-6

A risk assessment for this chemical is under review by an EPA work group.

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_II. CARCINOGENICITY ASSESSMENT FOR LIFETIME EXPOSURE

Substance Name -- Trichloroethylene
CASRN -- 79-01-6
Last Revised -- 07/01/89

__II.A.

The carcinogen assessment summary for this substance has been withdrawn following further review. A new carcinogen summary is in preparation by the CRAVE Work Group.

Contact: Rita S. Schoeny / ORD / FTS/684-7544 or 513/569-7544

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_III. HEALTH HAZARD ASSESSMENTS FOR VARIED EXPOSURE DURATIONS

Substance Name -- Trichloroethylene
CASRN -- 79-01-6

Not available at this time

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_IV. U.S. EPA REGULATORY ACTIONS

Substance Name -- Trichloroethylene
CASRN -- 79-01-6
Last Revised -- 03/01/88

EPA risk assessments may be updated as new data are published and as assessment methodologies evolve. Regulatory actions are frequently not updated at the same time. Compare the dates for the regulatory actions in this section with the verification dates for the risk assessments in sections I and II, as this may explain inconsistencies. Also note that some regulatory actions consider factors not related to health risk, such as technical or economic feasibility. Such considerations are indicated for each action. In addition, not all of the regulatory actions listed in this section involve enforceable federal standards. Please direct any questions you may have concerning these regulatory actions to the U.S. EPA contact listed for that particular action. Users are strongly urged to read the background information on each regulatory action in Background Document 4 in Service Code 5.

<<< Trichloroethylene >>>

__IV.A. CLEAN AIR ACT (CAA)

___IV.A.1. CAA REGULATORY DECISION

Action -- Intent to list under Section 112

Considers technological or economic feasibility? -- NO

Discussion -- Trichloroethylene (TCE) is a probable human carcingen (EPA Group B2) and according to EPA's preliminary risk assessment from ambient air exposures, public health risks are significant (4.1 cancer cases/year and maximum lifetime individual risks of 9.4xE-5). Thus, EPA indicated that it intends to add TCE to the list of hazardous air pollutants for which it intends to establish emission standards under section 112(b)(1)(A) of the Clean Air Act. The EPA will decide whether to add TCE to the list only after studying possible techniques that might be used to control emissions and further assessing the public health risks. The EPA will add TCE to the list if emissions standards are warranted.

Reference -- 50 FR 52422 (12/23/85)

EPA Contact -- Emissions Standards Division, OAQPS
(917)541-5571 / FTS 629-5571

------<<< Trichloroethylene >>>------

__IV.B. SAFE DRINKING WATER ACT (SDWA)

___IV.B.1. MAXIMUM CONTAMINANT LEVEL GOAL (MCLG) for Drinking Water

Value (status) -- 0 mg/L (Proposed, 1985)

Considers technological or economic feasibility? -- NO

Discussion -- An MCLG of 0 mg/L for trichloroethylene is proposed based on carcinogenic effects. Significant increases in the incidence of liver tumors have been reported in B6C3F1 mice of both sexes. Malignant lymphomas and pulmonary adenocarcinomas were also reported in mice. EPA has classified trichloroethylene in Group B2: sufficient evidence in animals and inadequate evidence in humans.

Reference -- 50 FR 46880 Part III (11/13/85)

EPA Contact -- Criteria and Standards Division, ODW /
(202)382-7571 / FTS 382-7571; or Drinking Water Hotline / (800)426-4791

<<< Trichloroethylene >>>

___IV.B.2. MAXIMUM CONTAMINANT LEVEL (MCL) for Drinking Water

Value (status) -- 5 ug/L (Final, 1987)

Considers technological or economic feasibility? -- YES

Discussion --

Reference -- 52 FR 35690

EPA Contact -- Criteria and Standards Division, ODW /
(202)382-7571 / FTS 382-7571; or Drinking Water Hotline / (800)426-4791

------<<< Trichloroethylene >>>------

__IV.C. *CLEAN WATER ACT (CWA)*

___IV.C.1. AMBIENT WATER QUALITY CRITERIA, Human Health

Water and Fish Consumption -- 2.7E+0 ug/L

Fish Consumption Only -- 8.07E+1 ug/L

Considers technological or economic feasibility? -- NO

Discussion -- For the maximum protection from the potential carcinogenic properties of this chemical, the ambient water concentration should be zero. However, zero may not be attainable at this time, so the recommended criteria represents a E-6 estimated incremental increase of cancer risk over a lifetime.

Reference -- 45 FR 79318 (11/28/80)

EPA Contact -- Criteria and Standards Division, OWRS
(202)475-7315 / FTS 475-7315

<<< Trichloroethylene >>>

___IV.C.2. AMBIENT WATER QUALITY CRITERIA, Aquatic Organisms

Freshwater:

Acute LEC -- 4.5E+4 ug/L
Chronic LEC -- None

Marine:

Acute LEC -- 2.0E+3 ug/L
Chronic LEC -- None

Considers technological or economic feasibility? -- NO

Discussion -- The values that are indicated as "LEC" are not criteria, but are the lowest effect levels found in the literature. LECs are given when the minimum data required to derive water quality criteria are not available.

Reference -- 45 FR 79318 (11/28/80)

EPA Contact -- Criteria and Standards Division, OWRS
(202)475-7315 / FTS 475-7315

------<<< Trichloroethylene >>>------

__IV.D. FEDERAL INSECTICIDE, FUNGICIDE, AND RODENTICIDE ACT (FIFRA)

No data available

------<<< Trichloroethylene >>>------

__IV.E. TOXIC SUBSTANCES CONTROL ACT (TSCA)

No data available

------<<< Trichloroethylene >>>------

__IV.F. RESOURCE CONSERVATION AND RECOVERY ACT (RCRA)

___IV.F.1. RCRA APPENDIX IX, for Ground Water Monitoring

Status -- Listed

Reference -- 52 FR 25942 (07/09/87)

EPA Contact -- Jerry Garman / OSW / (202)382-4658 / FTS 382-4658

------<<< Trichloroethylene >>>------

__IV.G. SUPERFUND (CERCLA)

___IV.G.1. REPORTABLE QUANTITY (RQ) for Release into the Environment

Value (status) -- 100 pounds (Proposed, 1987)

Considers technological or economic feasibility? -- NO

Discussion -- The proposed RQ for trichloroethylene is 100 pounds, based on potential carcinogenicity. The available data indicate a hazard ranking of low, based on a potency factor of 0.070 (mg/kg/day)-1 and weight-of-evidence classification B2, which corresponds to an RQ of 100 pounds.

Reference -- 52 FR 8140 (03/16/87)

EPA Contact -- RCRA/Superfund Hotline
(800)424-9346 / (202)382-3000 / FTS 382-3000

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_V. SUPPLEMENTARY DATA

Substance Name -- Trichloroethylene
CASRN -- 79-01-6

Not available at this time

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_VI. BIBLIOGRAPHY

Substance Name -- Trichloroethylene
CASRN -- 79-01-6

Not available at this time

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SYNONYMS

79-01-6
ACETYLENE TRICHLORIDE
ALGYLEN
ANAMENTH
BENZINOL
BLACOSOLV
BLANCOSOLV
CECOLENE
CHLORILEN
1-CHLORO-2,2-DICHLOROETHYLENE
CHLORYLEA
CHLORYLEN
CHORYLEN
CIRCOSOLV
CRAWHASPOL
DENSINFLUAT

1,1-DICHLORO-2-CHLOROETHYLENE
DOW-TRI
DUKERON
ETHINYL TRICHLORIDE
ETHYLENE TRICHLORIDE
ETHYLENE, TRICHLORO-
FLECK-FLIP
FLOCK FLIP
FLUATE
GEMALGENE
GERMALGENE
LANADIN
LETHURIN
NARCOGEN
NARKOGEN
NARKOSOID
NCI-C04546
NIALK
PERM-A-CHLOR
PERM-A-CLOR
PETZINOL
PHILEX
RCRA WASTE NUMBER U228
TCE
THRETHYLEN
THRETHYLENE
TRETHYLENE
TRI
TRIAD
TRIAL
TRIASOL
TRICHLOORETHEEN
TRICHLOORETHYLEEN, TRI
TRICHLORAETHEN
TRICHLORAETHYLEN, TRI
TRICHLORAN
TRICHLOREN
TRICHLORETHENE
TRICHLORETHYLENE
TRICHLORETHYLENE, TRI
TRICHLOROETHENE
Trichloroethylene
1,1,2-TRICHLOROETHYLENE
1,2,2-TRICHLOROETHYLENE
TRI-CLENE
TRICLORETENE
TRICLOROETILENE
TRIELENE
TRIELIN
TRIELINA
TRIKLONE
TRILEN
TRILENE
TRILINE

TRIMAR
TRIOL
TRI-PLUS
TRI-PLUS M
UN 1710
VESTROL
VITRAN
WESTROSOL

C-8 (h) TOLUENE

The attached Integrated Risk Information System (IRIS) printout (March 1990) is provided as a technical summary.

Toluene; CASRN 108-88-3 (07/01/89)

Health risk assessment information on a chemical is included in IRIS only after a comprehensive review of chronic toxicity data by work groups composed of U.S. EPA scientists from several Program Offices. The summaries presented in Sections I and II represent a consensus reached in the review process. The other sections contain U.S. EPA information which is specific to a particular EPA program and has been subject to review procedures prescribed by that Program Office. The regulatory actions in Section IV may not be based on the most current risk assessment, or may be based on a current, but unreviewed, risk assessment, and may take into account factors other than health effects (e.g., treatment technology). When considering the use of regulatory action data for a particular situation, note the date of the regulatory action, the date of the most recent risk assessment relating to that action, and whether technological factors were considered. Background information and explanations of the methods used to derive the values given in IRIS are provided in the five Background Documents in Service Code 5, which correspond to Sections I through V of the chemical files.

STATUS OF DATA FOR Toluene

File On-Line 01/31/87

Category (section)	Status	Last Revised
Oral RfD Assessment (I.A.)	on-line	03/01/88
Inhalation RfD Assessment (I.B.)	pending	
Carcinogenicity Assessment (II.)	on-line	02/01/89
Drinking Water Health Advisories (III.A.)	no data	
U.S. EPA Regulatory Actions (IV.)	on-line	03/01/88

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_I. CHRONIC HEALTH HAZARD ASSESSMENT FOR NONCARCINOGENIC EFFECTS

Substance Name -- Toluene
CASRN -- 108-88-3
Last Revised -- 03/01/88

The Reference Dose (RfD) is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis, but may not exist for other toxic effects such as carcinogenicity. In general, the RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Please refer to Background Document 1 in Service Code 5 for an elaboration of these concepts. RfDs can also be derived for the noncarcinogenic health effects of compounds which are also carcinogens. Therefore, it is essential to refer to other sources of information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file when a review of that evaluation is completed.

<<< Toluene >>>

__I.A. REFERENCE DOSE FOR CHRONIC ORAL EXPOSURE (RfDo)

NOTE: The Oral RfD for Toluene may change in the near future pending the outcome of a further review now being conducted by the Oral RfD Workgroup.

___I.A.1. ORAL RfD SUMMARY

Critical Effect	Experimental Doses*	UF	MF	RfD
Clinical chemistry and hematological parameters	NOAEL: 300 ppm (1130 MG/CU.m) converted to 29 mg/kg/day	100	1	3E-1 mg/kg/day
Rat Chronic Inhalation Study	LOAEL: none			
CITT, 1980				

*Dose Conversion Factors & Assumptions: 5 days/7 days, 6 hour/24 hour; 0.5 absorption factor, 20 cu.m human breathing rate; 70 kg; thus, 1130 mg/cu.m x 5 day/7 days x 6 hours/24 hours x 0.5 x 20 cu.m/day / 70 kg = 28.8 mg/kg/day

<<< Toluene >>>

___I.A.2. PRINCIPAL AND SUPPORTING STUDIES (ORAL RfD)

CIIT (Chemical Industry Institute of Toxicology). 1980. A 24-month inhalation toxicology study in Fischer-344 rats exposed to atmospheric toluene. CIIT, Research Triangle Park, NC.

Toluene is most likely a potential source of respiratory hazard. The only chronic toxicity study on toluene was conducted for 24 months in male and female F344 rats (CIIT, 1980). Toluene was administered by inhalation at 30, 100, or 300 ppm (113, 377, or 1130 mg/cu.m) to 120 male and 120 female F344 rats for 6 hours/day, 5 days/week. The same number of animals (120 males and 120 females) was used as a control. Clinical chemistry, hematology and urinalysis testing was conducted at 18 and 24 months. All parameters measured at the termination of the study were normal except for a dose-related reduction in hematocrit values in females exposed to 100 and 300 ppm toluene.

Based on these findings, a NOAEL of 300 ppm or 1130 mg/cu.m was derived. An oral RfD of 20 mg/day can be derived using route-to-route extrapolation. This was done by expanding the exposure from 6 hours/day, 5 days/week to continuous exposure and multiplying by 20 cu.m/day and 0.5 to reflect a 50% absorption factor.

<<< Toluene >>>

___I.A.3. UNCERTAINTY AND MODIFYING FACTORS (ORAL RfD)

UF = 100. An uncertainty factor of 100 (10 for sensitive individuals and 10 for intraspecies extrapolation) was also applied.

MF = 1

___I.A.4. ADDITIONAL COMMENTS (ORAL RfD)

Subchronic inhalation and subchronic oral studies in both mice and rats support the chosen NOAEL (NTP, 1981, 1982). Furthermore, an oral study (Wolf et al., 1956) contains subchronic data in which no adverse effects of toluene were reported at the highest dose tested (590 mg/kg/day).

___I.A.5. CONFIDENCE IN THE ORAL RfD

Study: High
Data Base: Medium
RfD: Medium

Confidence in the principal study is high because a large number of animals/sex were tested in each of three dose groups and many parameters were studied. Interim kills were performed. The data base is rated medium because several studies support the chosen effect level. The confidence of the RfD is not higher than medium because the critical study was by the inhalation route.

<<< Toluene >>>

___I.A.6. EPA DOCUMENTATION AND REVIEW OF THE ORAL RfD

Limited Peer Review and Agency-wide Internal Review, 1984.

U.S. EPA. 1985. Drinking Water Criteria Document for Toluene. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Drinking Water, Washington, DC.

Agency RfD Work Group Review: 05/20/85, 08/05/85, 08/05/86

Verification Date: 05/20/85

___I.A.7. EPA CONTACTS (ORAL RfD)

Christopher T. DeRosa / ORD -- (513)569-7534 / FTS 684-7534

Michael L. Dourson / ORD -- (513)569-7544 / FTS 684-7544

------<<< Toluene >>>------

__I.B. REFERENCE DOSE FOR CHRONIC INHALATION EXPOSURE (RfDi)

A risk assessment for this chemical is under review by an EPA work group.

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_II. CARCINOGENICITY ASSESSMENT FOR LIFETIME EXPOSURE

Substance Name -- Toluene
CASRN -- 108-88-3
Last Revised -- 02/01/89

Section II provides information on three aspects of the carcinogenic risk assessment for the agent in question; the U.S. EPA classification, and quantitative estimates of risk from oral exposure and from inhalation exposure. The classification reflects a weight-of-evidence judgment of the likelihood that the agent is a human carcinogen. The quantitative risk estimates are presented in three ways. The slope factor is the result of application of a low-dose extrapolation procedure and is presented as the risk per mg/kg/day. The unit risk is the quantitative estimate in terms of either risk per ug/L drinking water or risk per ug/cu.m air breathed. The third form in which risk is presented is a drinking water or air concentration providing cancer risks of 1 in 10,000, 1 in 100,000 or 1 in 1,000,000. Background Document 2 (Service Code 5) provides details on the rationale and methods used to derive the carcinogenicity values found in IRIS. Users are referred to Section I for information on long-term toxic effects other than carcinogenicity.

<<< Toluene >>>

__II.A. EVIDENCE FOR CLASSIFICATION AS TO HUMAN CARCINOGENICITY

___II.A.1. WEIGHT-OF-EVIDENCE CLASSIFICATION

Classification -- D; not classified

Basis -- No human data and inadequate animal data. Toluene did not produce positive results in the majority of genotoxic assays.

___II.A.2. HUMAN CARCINOGENICITY DATA

None.

<<< Toluene >>>

___II.A.3. ANIMAL CARCINOGENICITY DATA

A chronic (106-week) bioassay of toluene in F344 rats of both sexes reported no carcinogenic responses (CIIT, 1980). A total of 960 rats were exposed by inhalation for 6 hours/day, 5 days/week to toluene at 0, 30, 100, or 300 ppm. Groups of 20/sex/dose were sacrificed at 18 months. Gross and microscopic examination of tissues and organs identified no increase in neoplastic tissue or tumor masses among treated rats when compared with controls. The study is considered inadequate because the highest dose administered was well below the MTD for toluene and because of the high incidence of lesions and pathological changes in the control animals.

Several studies have examined the carcinogenicity of toluene following repeated dermal applications. Toluene (dose not reported) applied to shaved interscapular skin of 54 male mice (strains A/He, C3HeB, SWR) throughout their lifetime (3 times weekly) produced no carcinogenic response (Poel, 1963). One drop of toluene (about 6 mL) applied to the dorsal skin of 20 random-bred albino mice twice weekly for 50 weeks caused no skin papillomas or carcinomas after a 1-year latency period was allowed (Coombs et al., 1973). No increase in the incidence of skin or systemic tumors was demonstrated in male or female mice of three strains (CF, C3H, or CBaH) when toluene was applied to the back of 25 mice of each sex of each strain at 0.05-0.1 mL/mouse, twice weekly for 56 weeks (Doak et al., 1976). One skin papilloma and a single skin carcinoma were reported among a group of 30 mice treated dermally with one drop of 0.2% (w/v) solution toluene twice weekly, administered from droppers delivering 16-20 uL per drop for 72 weeks (Lijinsky and Garcia, 1972). It is not reported whether evaporation of toluene from the skin was prevented during these studies.

<<< Toluene >>>

___II.A.4. SUPPORTING DATA FOR CARCINOGENICITY

Toluene was found to be nonmutagenic in reverse mutation assays with S. typhimurium (Mortelmans and Riccio, 1980; Nestman et al., 1980; Bos et al., 1981; Litton Bionetics, Inc., 1981; Snow et al., 1981) and E. coli (Mortelmans and Riccio, 1980), with and without metabolic activation. Toluene did not induce mitotic gene conversion (Litton Bionetics, Inc., 1981; Mortelmans and Riccio, 1980) or mitotic crossing over (Mortelmans and Riccio, 1980) in S. cerevisiae. Although Litton Bionetics, Inc. (1981) reported that toluene did not cause increased chromosomal aberrations in bone marrow cells, several Russian studies (Dobrokhotov, 1972; Lyapkalo, 1973) report toluene as effective in causing chromosal damage in bone marrow cells of rats. There was no evidence of chromosomal aberrations in blood lymphocytes of workers exposed to toluene only (Maki-Paakkanen et al., 1980; Forni et al., 1971), although a slight increase was noted in workers exposed to toluene and benzene (Forni et al., 1971; Funes-Craviota et al., 1977). This is supported by studies of cultured human lymphocytes exposed to toluene in vitro. No elevation of chromosomal aberrations or sister chromatid exchanges was observed (Gerner-Smidt and Friedrich, 1978).

__II.B. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM ORAL EXPOSURE

Not available.

__II.C. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM INHALATION EXPOSURE

Not available.

__II.D. EPA DOCUMENTATION, REVIEW, AND CONTACTS (CARCINOGENICITY ASSESSMENT)
<<< Toluene >>>

___II.D.1. EPA DOCUMENTATION

U.S. EPA. 1987. Drinking Water Criteria Document for Toluene. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Drinking Water, Washington, DC. ECAO-CIN-408.

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Funes-Cravioto, F., B. Kolmodin-hedman, J. Lindsten, et al. 1977. Chromosome aberrations and sister-chromatid exchange in workers in chemical laboratories and a rotoprinting factory and in children of women laboratory workers. Lancet. 2: 322-325.

Gerner-Smidt, P. and U. Friedrich. 1978. The mutagenic effect of benzene, toluene and xylene studied by the SCE technique. Mutat. Res. 58(2-3): 313-316.

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Poel, W.E. 1963. Skin as a test site for the bioassay of carcinogens and carcinogen precursors. Natl. Cancer Inst. Monogr. 10: 611-625.

Snow, L., P. MacNair and B.C. Casto. 1981. Mutagenesis testing of toluene in Salmonella strains TA100 and TA98. Report prepared for the U.S. EPA by Northrup Services, Inc., Research Triangle park, NC.

___II.D.2. REVIEW (CARCINOGENICITY ASSESSMENT)

The values in the 1987 Drinking Water Criteria Document for Toluene have received peer and administrative review.

Agency Work Group Review: 09/15/87

Verification Date: 09/15/87

___II.D.3. U.S. EPA CONTACTS (CARCINOGENICITY ASSESSMENT)

Dharm V. Singh / ORD -- (202)382-5958 / FTS 382-5958

Robert E. McGaughy / ORD -- (202)382-5898 / FTS 382-5898

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_III. HEALTH HAZARD ASSESSMENTS FOR VARIED EXPOSURE DURATIONS

Substance Name -- Toluene
CASRN -- 108-88-3

Not available at this time

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_IV. U.S. EPA REGULATORY ACTIONS

Substance Name -- Toluene
CASRN -- 108-88-3
Last Revised -- 03/01/88

EPA risk assessments may be updated as new data are published and as assessment methodologies evolve. Regulatory actions are frequently not updated at the same time. Compare the dates for the regulatory actions in this section with the verification dates for the risk assessments in sections I and II, as this may explain inconsistencies. Also note that some regulatory actions consider factors not related to health risk, such as technical or economic feasibility. Such considerations are indicated for each action. In addition, not all of the regulatory actions listed in this section involve enforceable federal standards. Please direct any questions you may have concerning these regulatory actions to the U.S. EPA contact listed for that particular action. Users are strongly urged to read the background information on each regulatory action in Background Document 4 in Service Code 5.

<<< Toluene >>>

__IV.A. CLEAN AIR ACT (CAA)

___IV.A.1. CAA REGULATORY DECISION

Action -- Decision not to regulate

Considers technological or economic feasibility? -- NO

Discussion -- The U.S. EPA concluded that current information does not indicate that toluene endangers public health at ambient concentrations (excluding emergency releases), and thus no regulation directed specifically at toluene is necessary at this time under the CAA.

Reference -- 45 FR 22195 (05/25/84).

EPA Contact -- Emissions Standards Division, OAQPS
(917)541-5571 / FTS 629-5571

------<<< Toluene >>>------

__IV.B. SAFE DRINKING WATER ACT (SDWA)

___IV.B.1. MAXIMUM CONTAMINANT LEVEL GOAL (MCLG) for Drinking Water

Value (status) -- 2.0 mg/L (Proposed, 1985)

Considers technological or economic feasibility? -- NO

Discussion -- An MCLG of 2.0 mg/L for toluene is proposed based on a DWEL of 10.1 mg/L and an assumed contribution of 20% from drinking water. A DWEL of 10.1 mg/L was calculated from a NOAEL of 1130 mg/cu.m (highest dose tested) for lung effects in rats (2-year inhalation study), with an uncertainty factor of 100 applied and an assumed 50% pulmonary absorption rate.

Reference -- 50 FR 46936 Part IV (11/13/85)

EPA Contact -- Krishan Khanna / Criteria and Standards Division, ODW /
(202)382-7571 / FTS 382-7571; or Drinking Water Hotline / (800)426-4791

------<<< Toluene >>>------

__IV.C. CLEAN WATER ACT (CWA)

___IV.C.1. AMBIENT WATER QUALITY CRITERIA, Human Health

Water and Fish Consumption: 14.3 mg/L

Fish Consumption Only: 424 mg/L

Considers technological or economic feasibility? -- NO

Discussion -- The WQC of 14.3 mg/L is based on consumption of contaminated aquatic organisms and water. A WQC of 424 mg/L has also been established based on consumption of contaminated aquatic organisms alone.

Reference -- 45 FR 79318 (11/28/80)

EPA Contact -- Criteria and Standards Division / OWRS / (202)475-7315 / FTS 475-7315

<<< Toluene >>>

___IV.C.2. AMBIENT WATER QUALITY CRITERIA, Aquatic Organisms

Freshwater:

Acute -- 17,500 ug/L (LEL)
Chronic -- None

Marine:

Acute -- 6300 ug/L (LEL)
Chronic -- 5000 ug/L (LEL)

Considers technological or economic feasibility? -- NO

Discussion -- Water quality criteria for the protection of aquatic life are derived from a minimum data base of acute and chronic tests on a variety of aquatic organisms. The "(LEL)" after the value indicates that the minimum data were not available and the concentration given is not a criteria value but the lowest effect level found in the literature.

Reference -- 45 FR 79318 (11/28/80)

EPA Contact -- Criteria and Standards Division / OWRS / (202)475-7315 / FTS 475-7315

------<<< Toluene >>>------

__IV.D. FEDERAL INSECTICIDE, FUNGICIDE, AND RODENTICIDE ACT (FIFRA)

No data available

------<<< Toluene >>>------

__IV.E. TOXIC SUBSTANCES CONTROL ACT (TSCA)

No data available

------<<< Toluene >>>------

__IV.F. RESOURCE CONSERVATION AND RECOVERY ACT (RCRA)

___IV.F.1. RCRA APPENDIX IX, for Ground Water Monitoring

Status -- Listed

Reference -- 52 FR 25942 (07/09/87)

EPA Contact -- Jerry Garman / OSW / (202)382-4658 / FTS 382-4658

------<<< Toluene >>>------

__IV.G. SUPERFUND (CERCLA)

___IV.G.1. REPORTABLE QUANTITY (RQ) for Release into the Environment

Value (status) -- 1000 pounds (Final, 1985)

Considers technological or economic feasibility? -- NO

Discussion -- The final RQ is based on aquatic toxicity, as established under Section 311(b)(4) of the Clean Water Act, ignitability, and chronic toxicity. Available data indicate that the aquatic 96-Hour Median Threshold Limit for Toluene is between 10 and 100 ppm. Its closed-cup flash point is less than 100F and its boiling point is >100F. RQ assignments based on chronic toxicity reflect two primary attributes of the hazardous substance, the minimum effective dose (MED) levels for chronic exposure (mg/day for a 70-kg person) and the type of effect (liver necrosis, teratogenicity, etc). A composite score is determined from an evaluation of these two attributes. Toluene was determined to have a composite score between 6 and 20, corresponding to a chronic toxicity RQ of 1000 pounds.

Reference -- 50 FR 13456 (04/04/85)

EPA Contact -- RCRA/Superfund Hotline
(800)424-9346 / (202)382-3000 / FTS 382-3000

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_V. SUPPLEMENTARY DATA

Substance Name -- Toluene
CASRN -- 108-88-3

Not available at this time

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_VI. BIBLIOGRAPHY

Substance Name -- Toluene
CASRN -- 108-88-3

Not available at this time

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SYNONYMS

108-88-3
ANTISAL 1a
BENZENE, METHYL
METHACIDE
METHYL-BENZENE
METHYLBENZOL
NCI-C07272
PHENYL-METHANE
RCRA WASTE NUMBER U220
TOLUEEN
TOLUEN
Toluene
TOLUOL
TOLUOLO
TOLU-SOL
UN 1294

C-8 (i) VINYL CHLORIDE

The attached "Health Effects Assessment for Vinyl Chloride" (USEPA, 1984a) is provided as a technical summary.

PB86-134475
EPA/540/1-86/036
September 1984

HEALTH EFFECTS ASSESSMENT FOR VINYL CHLORIDE

U.S. Environmental Protection Agency
Office of Research and Development
Office of Health and Environmental Assessment
Environmental Criteria and Assessment Office
Cincinnati, OH 45268

U.S. Environmental Protection Agency
Office of Emergency and Remedial Response
Office of Solid Waste and Emergency Response
Washington, DC 20460

DISCLAIMER

This report has been funded wholly or in part by the United States Environmental Protection Agency under Contract No. 68-03-3112 to Syracuse Research Corporation. It has been subject to the Agency's peer and administrative review, and it has been approved for publication as an EPA document. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

PREFACE

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with vinyl chloride. All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered as preliminary and reflect limited resources allocated to this project. Pertinent toxicologic and environmental data were located through on-line literature searches of the Chemical Abstracts, TOXLINE, CANCERLINE and the CHEMFATE/DATALOG data bases. The basic literature searched supporting this document is current up to September, 1984. Secondary sources of information have also been relied upon in the preparation of this report and represent large-scale health assessment efforts that entail extensive peer and Agency review. The following Office of Health and Environmental Assessment (OHEA) sources have been extensively utilized:

U.S. EPA. 1980a. Ambient Water Quality Criteria for Vinyl Chloride. Environmental Criteria and Assessment Office, Cincinnati, OH. EPA 440/5-80-078. NTIS PB 81-117889.

U.S. EPA 1982. Health and Environmental Effects Profile for Vinyl Chloride. Prepared by the Environmental Criteria and Assessment Office, Cincinnati, OH, OHEA for the Office of Solid Waste and Emergency Response, Washington, DC.

U.S. EPA. 1983a. Reportable Quantity Document for Vinyl Chloride. Prepared by the Environmental Criteria and Assessment Office, Cincinnati, OH, OHEA for the Office of Solid Waste and Emergency Response, Washington, DC.

U.S. EPA. 1983b. Review of Toxicologic Data in Support of Evaluation for Carcinogenic Potential of: Vinyl Chloride. Prepared by the Carcinogen Assessment Group, OHEA, Washington, DC for the Office of Solid Waste and Emergency Response, Washington, DC.

The intent in these assessments is to suggest acceptable exposure levels whenever sufficient data were available. Values were not derived or larger uncertainty factors were employed when the variable data were limited in scope tending to generate conservative (i.e., protective) estimates. Nevertheless, the interim values presented reflect the relative degree of hazard associated with exposure or risk to the chemical(s) addressed.

Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, the AIS or acceptable intake subchronic, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval (i.e., for an interval that does not constitute a significant portion of the lifespan). This type of exposure estimate has not been extensively used or rigorously defined, as previous risk assessment efforts have been primarily directed towards exposures from toxicants in ambient air or water where lifetime exposure is assumed. Animal data used for AIS estimates generally include exposures with durations of 30-90 days. Subchronic human data are rarely available. Reported exposures are usually from chronic occupational exposure situations or from reports of acute accidental exposure.

The AIC, acceptable intake chronic, is similar in concept to the ADI (acceptable daily intake). It is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan [see U.S. EPA (1980b) for a discussion of this concept]. The AIC is route specific and estimates acceptable exposure for a given route with the implicit assumption that exposure by other routes is insignificant.

Composite scores (CSs) for noncarcinogens have also been calculated where data permitted. These values are used for ranking reportable quantities; the methodology for their development is explained in U.S. EPA (1983c).

For compounds for which there is sufficient evidence of carcinogenicity, AIS and AIC values are not derived. For a discussion of risk assessment methodology for carcinogens refer to U.S. EPA (1980b). Since cancer is a process that is not characterized by a threshold, <u>any</u> exposure contributes an increment of risk. Consequently, derivation of AIS and AIC values would be inappropriate. For carcinogens, q_1^*s have been computed based on oral and inhalation data if available.

ABSTRACT

In order to place the risk assessment evaluation in proper context, refer to the preface of this document. The preface outlines limitations applicable to all documents of this series as well as the appropriate interpretation and use of the quantitative estimates presented.

Vinyl chloride following inhalation exposure has been shown to be carcinogenic in humans, rats, mice and hamsters. Using data for tumor incidence in rats, a q_1^* for humans of 2.5×10^{-2} $(mg/kg/day)^{-1}$ was estimated.

No data are available concerning oral exposure in humans and cancer risk. On the basis of total tumors in female rats fed vinyl chloride-containing diets, a human q_1^* of 2.3 $(mg/kg/day)^{-1}$ was estimated for oral exposure.

ACKNOWLEDGEMENTS

The initial draft of this report was prepared by Syracuse Research Corporation under Contract No. 68-03-3112 for EPA's Environmental Criteria and Assessment Office, Cincinnati, OH. Dr. Christopher DeRosa and Karen Blackburn were the Technical Project Monitors and Helen Ball was the Project Officer. The final documents in this series were prepared for the Office of Emergency and Remedial Response, Washington, DC.

Scientists from the following U.S. EPA offices provided review comments for this document series:

Environmental Criteria and Assessment Office, Cincinnati, OH
Carcinogen Assessment Group
Office of Air Quality Planning and Standards
Office of Solid Waste
Office of Toxic Substances
Office of Drinking Water

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LIST OF ABBREVIATIONS

ADI	Acceptable daily intake
AIC	Acceptable intake chronic
AIS	Acceptable intake subchronic
bw	Body weight
CAS	Chemical abstract service
CNS	Central nervous system
CS	Composite score
FEL	Frank-effect level
GOT	Glutamic oxaloacetic transaminase
GPT	Glutamic pyruvic transaminase
LOAEL	Lowest-observed-adverse-effect level
MED	Minimum effective dose
NOAEL	No-observed-adverse-effect level
NOEL	No-observed-effect level
ppm	Parts per million
PVC	Polyvinyl chloride
TLV	Threshold limit value
TWA	Time-weighted average
VCM	Vinyl chloride monomer

1. ENVIRONMENTAL CHEMISTRY AND FATE

The relevant physical and chemical properties and environmental fate of vinyl chloride (CAS No. 75-01-4), also known as chloroethene, are given below.

Chemical class:	halogenated aliphatic hydrocarbon (purgeable halocarbon)
Molecular weight:	62.5
Vapor pressure:	2660 mm Hg at 25°C (Callahan et al., 1979)
Water solubility:	2760 mg/ℓ at 25°C (Horvath, 1982)
	1100 mg/kg at 28°C (U.S. EPA, 1980a)
Octanol/water partition coefficient:	24 (estimated) (U.S. EPA, 1980a)
Bioconcentration factor:	2.97 (estimated) (U.S. EPA, 1980a)
Half-lives in	
Air:	1.2 days (Singh et al., 1981)
Water:	several minutes to a few hours (Callahan et al., 1979) 1-5 days (estimated)

The estimated half-life values for vinyl chloride in aquatic media have been derived from the reaeration rate ratio (0.675) and the oxygen reaeration rate of 0.19-0.96 day^{-1} given by Mabey et al. (1981).

The fate of vinyl chloride in soil is not known with certainty. Evaporation is expected to be the predominant loss mechanism from the soil surface. The half-life for soil evaporation should be longer than its evaporative half-life from water. Despite its expected low soil sorption rate and insignificant biodegradation rate (Callahan et al., 1979; Mabey et al., 1981), the probability of groundwater contamination through leaching of vinyl chloride from soil is low (Page, 1981).

2. ABSORPTION FACTORS IN HUMANS AND EXPERIMENTAL MAMMALS

2.1. ORAL

Although quantitative data are not available, Withey (1976) and Watanabe et al. (1976a) have reported rapid absorption of vinyl chloride from the gastrointestinal tract into the blood of dosed rats.

2.2. INHALATION

Rapid absorption and equilibration of vinyl chloride from the lungs into the bloodstream have been reported for rats exposed to the compound by inhalation (Duprat et al., 1977; Watanabe et al., 1976b; Bolt et al., 1977). Within 10 minutes following inhalation exposure of rats to 20,000 ppm of [^{14}C] vinyl chloride for 5 minutes, [^{14}C] was found in several tissues of the exposed animals (Duprat et al., 1977). In a brief review of a study regarding the inhalation uptake of vinyl chloride by rats (Withey and Collins, 1976), the U.S. EPA (1980a) stated that in 200 g rats, the concentration of vinyl chloride in blood produced by intaking 1.97 ppm was equivalent to that produced by gavage treatment with 4.5 mg/kg/day. This relationship held true for gavage doses ranging from 2-25 mg/kg/day.

3. TOXICITY IN HUMANS AND EXPERIMENTAL ANIMALS

3.1. SUBCHRONIC

3.1.1. Oral. Feron et al. (1975) administered vinyl chloride monomer by gavage to groups of 15 male and 15 female Wistar rats at a level of 0, 30, 100 or 300 mg/kg bw, 6 days/week, for 13 weeks. Both males and females given the highest dose level had significantly increased liver-to-body weight ratios in the absence of hepatic damage. Males given the highest dose level also had significantly decreased adrenal-to-body weight ratio. Several hematological and biochemical changes were reported, but Feron et al. (1975) expressed reservations about the toxicological significance of these changes. The reported hematological and biochemical changes included a significantly decreased number of leucocytes in the mid- and high-dose groups of females; significantly decreased blood sugar in the mid- and high-dose groups of both sexes; and significantly decreased serum GOT, serum GPT and urinary GOT in the high-dose group of males. Hepatocellular rough endoplasmic reticulum of both sexes of high-dose groups was hypertrophic. No treatment-related effects were reported for the lowest dose groups. The authors considered 30 mg/kg to be the NOEL of this experiment but also stated that a somewhat higher no-effect level could be expected.

3.1.2. Inhalation. Several subchronic inhalation studies of vinyl chloride have been summarized by U.S. EPA (1983a). Due to the time limitations of this project, the subchronic studies discussed below were taken, in part, from that document.

A three-part subchronic inhalation study of rats, guinea pigs, rabbits and dogs revealed toxic effects in rats and rabbits exposed to 50-500 ppm of vinyl chloride, but not in guinea pigs or dogs (Torkelson et al., 1961). In the first part of the study, 10 male and 10 female rats were exposed to 500 ppm (1278 mg/m³) of vinyl chloride for 7 hours/day, 5 days/week, for 4.5 months. Five unexposed rats of each sex served as controls. This exposure level resulted in central lobular granular degeneration in the liver and interstitial and tubular changes in the kidneys. The average liver weight of both sexes of experimental animals was increased over controls; however, this increase was statistically significant in males only ($p=0.001$).

In the second part of the study, rats (20-24 males, 24 females), guinea pigs (10 male, 8 female), rabbits (3 male, 3 female) and dogs (1 male, 1 female) were exposed to 100 or 200 ppm (255.6 or 511.2 mg/m³) of vinyl chloride for 7 hours/day, 5 days/week, for 6 months. In addition, groups of five male rats were exposed to 100 or 200 ppm of vinyl chloride for 0.5, 1, 2 or 4 hours/ day, 5 days/week, for 6 months. Both unexposed and air-exposed controls were used for each species. At the 200 ppm, 7 hours/day level, the livers of both sexes of rabbits were affected by exposure to vinyl chloride, characterized by central lobular granular degeneration in both sexes and necrosis with foamy vacuolation in males or necrosis with periportal cellular infiltration in females. Increased mean liver weights were observed in male and female rats exposed to 100 or 200 ppm of vinyl chloride for 7 hours/day ($p<0.005$, as compared with controls).

In the third part of the study, rats (24 male, 24 female), guinea pigs (12 male, 12 female), rabbits (3 male, 3 female) and dogs (1 male, 1 female) were exposed to 50 ppm (127.8 mg/m³) of vinyl chloride for 7 hours/day, 5 days/week, for 6 months. In addition, groups of 10 male rats were exposed to 50 ppm of vinyl chloride for 1, 2 or 4 hours/day, 5 days/week, for 6 months. Both unexposed and air-exposed controls were used for each species.

for all species tested, there was no difference between treated or control animals in regard to mortality, growth, organ weights, or microscopic examination of tissues. This study suggests a NOEL for rats of 50 ppm and a LOAEL of 100 ppm of vinyl chloride for increased liver weights, and a NOEL for dogs and guinea pigs of 200 ppm of vinyl chloride.

A total of 27 CD-1 Charles River white male mice were exposed to 2500-6000 ppm (6391 or 15,337 mg/m³) of vinyl chloride for 5 hours/day, 5 days/week, for 5 or 6 months (Suzuki, 1978). Resultant alveologenic tumors in mice were examined by light and electron microscopy to characterize the toxic changes that occur before tumor formation. Suzuki (1980) reported a series of pathological changes including proliferation and hypertrophy of the terminal bronchiolar cells (ciliated and Clara cells), hyperplasia of the alveolar epithelium, degeneration of alveolar septal cells, and occasional peribronchiolar or bronchiolar inflammation. These changes occurred in the lungs of almost all of the treated mice, regardless of whether they were exposed to 2500 or 6000 ppm of vinyl chloride.

Sokal et al. (1980) investigated the effects of chronic inhalation exposure to vinyl chloride with male rats (strain and number not reported). The rats were exposed to 0, 50, 500 or 20,000 ppm of vinyl chloride for 5 hours/day, 5 days/week, for 10 months. Morphological lesions in the liver and testes, depression of body weight gain, increased organ weights, and slight hematological and biochemical changes in the blood were observed in treated animals. The abstract of this study did not distinguish between level of exposure and toxic effects, and the paper was not available for further review.

Following acute toxicity determinations for vinyl chloride, Prodan et al. (1975) studied the long-term effects of vinyl chloride in guinea pigs (strain and sex not reported) in a subchronic inhalation study. Groups of 10 guinea pigs were exposed to 0 or 10% (0 or 100,000 ppm; 0 or 255,624 mg/m³) vinyl chloride vapors for 2 hours/day for a period of 90 days. There was a statistically significant ($p<0.01$) slowed growth in exposed animals when compared to controls. Vinyl chloride had a narcotic effect on treated animals, resulting in decreased spontaneous activity. There was a significant increase in mean kidney weight in those guinea pigs exposed to 10% vinyl chloride, but the mean liver weight was similar to that of controls. Hepatocellular lesions covering the entire lobule but more dense toward the center, hepatocellular necrosis, and fibroblastic and Kupfferian proliferation were observed in the livers of experimental animals during histopathological examination. Moderate lesions of the glomeruli, marked lesions in the renal tubules, a strong cellular reaction in the spleen (marked by almost total disappearance of the red pulp), and pulmonary fibrosis were also noted in guinea pigs exposed to 10% vinyl chloride. Hematological parameters of treated animals paralleled those of control animals.

In another subchronic inhalation study, Lester et al. (1963) exposed groups of 15 male and 15 female Sherman rats to 0 or 2.0% (0 or 20,000 ppm; 0 or 51,125 mg/m³) vinyl chloride vapors for 8 hours/day, 5 days/week, for 3 months. No differences in body weight, hemoglobin values, hematocrit and prothrombin values, monocytes, eosinophils, or external appearance were noted between experimental and control animals. The only differences noted in rats exposed to 2% vinyl chloride in comparison to those not exposed to vinyl chloride were a significant increase in mean liver weight and a significant decrease in mean spleen weight. There was no evidence of tumorigenesis in any organs or tissues examined histopathologically.

3.2. CHRONIC

3.2.1. Oral. Feron et al. (1981) administered vinyl chloride monomer to five groups of 60-80 male and 60-80 female Wistar rats by incorporating polyvinyl chloride powder with a high content of vinyl chloride monomer into the diet or by gastric intubation of a 10% vinyl chloride monomer in soyabean oil. The dietary levels of vinyl chloride monomer provided doses of 0, 1.7, 5.0 and 14.1 mg/kg/day as determined by measured food consumption, and the gastric intubation dose level was 300 mg/kg bw given 5 days/week. Animals were treated for their lifespan. A dose-related increase in mortality was reported, with decreased survival at all dose levels. There was also an increase in a variety of neoplastic and non-neoplastic treatment-related hepatic lesions at all dose levels. Other treatment-related effects at the 14.1 mg/kg/day and 300 mg/kg bw levels included shortened blood-clotting times, slightly increased serum alpha-foetoprotein levels, hepatomegaly, and increased splenic hematopoietic activity. Feron et al. (1981) concluded that the NOEL for vinyl chloride to rats was <1.7 mg/kg/day, the lowest dose tested in this study.

3.2.2. Inhalation. Numerous chronic inhalation studies of vinyl chloride in humans and experimental animals have been summarized by U.S. EPA (1983a). Due to the time limitations of this project, the chronic studies discussed below were taken, in part, from that document.

There are numerous clinical indications that chronic inhalation exposure to vinyl chloride is toxic to humans (U.S. EPA, 1980a). Hepatitis-like changes, angioneurosis, Reynaud's syndrome, dermatitis, acro-osteolysis, thyroid insufficiency, and hepatomegaly have been reported (Cordier et al., 1966; Dinman et al., 1971; Filatova et al., 1958; Harris and Adams, 1967; Marsteller and Lebach, 1975; Tribukh et al., 1949; Wedrychowiez, 1976; Wilson et al., 1967). Other long-term effects include functional disturbances of the CNS with adrenergic sensory polyneuritis (Smirnova and Granik, 1970); thrombocytopenia, splenomegaly, liver malfunction with fibrosis, pulmonary changes (Lange et al., 1974); alterations in serum enzyme levels (Makk et al., 1976); portal hypertension attributed to an abnormality of the portal vein radicles, or hepatic sinusoids (Blendis et al., 1978); and angiosarcoma or fibrosis of the liver and acro-osteolysis, all of which are accompanied by microvascular abnormalities (Maricq et al., 1976).

Chronic inhalation studies of experimental animals exposed to vinyl chloride yield toxic effects similar to those seen in humans, involving the liver, spleen, kidneys, hematopoietic system and skeletal system. In a three-part study, Feron et al. (1979a,b) and Feron and Kroes (1979) investigated the toxic effects of chronic inhalation exposure to vinyl chloride in Wistar rats. Groups of 62 male and 62 female rats were exposed to 0 or 5000 ppm (0 or 12, 781 mg/m³) of vinyl chloride for 7 hours/day, 5 days/week, for 52 weeks. In the first part of the study, growth, mortality, hematology, clinical chemistry and organ weights were examined (Feron et al., 1979a). In rats exposed to 5000 ppm of vinyl chloride, treatment-related toxic effects included slight growth retardation; slightly shortened blood clotting time; increased potassium contents of the blood serum; increased blood nitrogen urea levels; increased kidney, heart and spleen weights; slight signs of anemia; and mortality. In the second part of the study, the experimental animals were examined for morphological changes in the respiratory tract, ceruminous glands, brain, kidneys, heart and spleen (Feron and

Kroes, 1979). Rats exposed to 5000 ppm of vinyl chloride had tubular nephrosis, mild focal degeneration of the myocardium, increased hematopoietic activity in the spleen, and tumors of the brain, lungs, ceruminous glands and nasal cavity. The third part of the study, in which the morphological changes in the liver were examined, indicated degenerative, hyperplastic and neoplastic changes (including hepatocellular carcinoma) in hepatic parenchyma, and angiosarcoma of the liver in rats after exposure to 5000 ppm of vinyl chloride (Feron et al., 1979b). It seems likely that the mortality observed among treated animals may have been due to the carcinogenic response. Neither a NOEL nor a NOAEL for vinyl chloride in rats can be suggested from this study, as the only exposure level tested (5000 ppm) was a FEL for increased mortality, among other effects.

Viola (1970) exposed groups of 25 male Wistar albino rats to 0 or 30,000 ppm of vinyl chloride (equivalent to 0 or 76,690 mg/m³) for 4 hours/day, 5 days/week, for 12 months. Histological examination was performed on the paws, brain, liver, kidneys and thyroid. Metatarsal bone metaplasia and chondroid metaplasia were observed in treated animals. The skin covering the paws was affected by epidermal hyperkeratosis, basal layer vacuolization and degeneration, disappearance of the cutaneous adnexa, and epidermal edema. Diffuse degenerative lesions of the grey and white matter of the brain and atrophy of the granular layer of the cerebellum were also observed in animals exposed to 30,000 ppm of vinyl chloride. The livers of treated animals were characterized by increased volume, diffused interstitial hepatitis, abnormal proliferation of Kupffer's cells (often hypertrophic) and partial necrosis. The kidneys were marked by signs of tubulonephrosis that were sometimes accompanied by chronic interstitial nephritis. The thyroid was affected by colloid goiter and an increase in parafollicular cells. Similar histopathological changes were not seen in the skeleton or organs of control animals. The only exposure level tested in this study (30,000 ppm) also represents a FEL.

3.3. TERATOGENICITY AND OTHER REPRODUCTIVE EFFECTS

3.3.1. Oral. *Pertinent data regarding the teratogenicity of orally* administered vinyl chloride could not be located in the available literature.

3.3.2. Inhalation. Vinyl chloride was not teratogenic when administered by inhalation to rats, mice or rabbits (Ungvary et al., 1978; John et al., 1977, 1981). The discussion of these studies that appears below was taken, in part, from U.S. EPA (1983a).

In a teratogenicity study in CFY rats, Ungvary et al. (1978) exposed groups of 13-28 pregnant rats to 0 or 4000 mg/m³ (~1500 ppm) vinyl chloride for 24 hours/day during days 1-9, 8-14 or 14-21 of gestation. Significantly increased (p~0.05) fetal mortality and fetotoxic effects were observed in the offspring of dams exposed to vinyl chloride during the first third of pregnancy (days 1-9 of gestation). Similar effects were not seen in offspring of dams exposed in the second or last third of pregnancy. No teratological effects related to vinyl chloride exposure were noted in any of the experimental groups.

John et al. (1977, 1981) performed a teratogenicity study with pregnant CF_1 mice, Sprague-Dawley rats and New Zealand white rabbits. Initially, groups of 30-40 bred mice, 20-35 bred rats and 15-20 bred rabbits were exposed to 500 ppm (~1278 mg/m³) vinyl chloride for 7 hours/day on days 6-15 (mice and rats) or 6-18 (rabbits) of gestation. Using the same exposure period, mice were subsequently exposed to 50 ppm (~128 mg/m³) vinyl chloride and rats and rabbits to 2500 ppm (~6390 mg/m³) vinyl chloride.

These exposures resulted in maternal toxicity, but no significant embryonal or fetal toxicity or gross teratogenic abnormalities were observed in the offspring of exposed dams. There were excess occurrences of minor skeletal abnormalities and increased fetal deaths at the higher exposure levels; however, neither of these effects occurred at a statistically significant increased incidence when compared with respective control animals.

3.4. TOXICANT INTERACTIONS

Metabolism of vinyl chloride by rats _in vivo_ is inhibited by pretreatment with ethanol or pyrazole, which is an inhibitor of alcohol dehydrogenase, xanthine oxidase and other enzymes (Hefner et al., 1975; Carter and Isselbacher, 1972). In rats, simultaneous chronic ingestion of ethanol and inhalation exposure to vinyl chloride increased the incidence of liver tumors and tumors in other sites as compared to the incidence expected for exposure to only vinyl chloride (Radike et al., 1977). Jaeger (1975) found that the effects on rats of 4-hour inhalation exposures to 200 ppm of vinylidene chloride and 1000 ppm of vinyl chloride were less severe than those seen after exposure to only 200 ppm of vinylidine chloride. The toxicological endpoint used for comparison was serum alanine α-ketoglutarate transaminase levels.

4. CARCINOGENICITY

4.1. HUMAN DATA

4.1.1. Oral. Pertinent data regarding the carcinogenicity of oral exposure to vinyl chloride in humans could not be located in the available literature.

4.1.2. Inhalation. Numerous case reports and epidemiology studies on the carcinogenicity of vinyl chloride to humans have been summarized by IARC (1979), U.S. EPA (1980a, 1983b) and Infante (1981). For the purposes of this document, only those studies presenting sufficient data on the exposed population and a substantial number of cancer cases have been reviewed for the assessment of carcinogenic risk. The exposure and cancer incidence data are summarized in Table 4-1. These data have been previously summarized by U.S. EPA (1983b).

Infante (1981) reviewed epidemiological data that indicate an association between liver cancer, brain cancer, lung cancer, and hematopoietic and lymphatic cancers and vinyl chloride exposure. Waxweiler et al. (1976) reported that 7 of 136 deaths among 1287 workers exposed to vinyl chloride for ≥5 years were due to biliary and liver cancer. All seven deaths occurred after a latency period of 15 years. The incidence of biliary and liver cancer among this group of workers was considered to be significantly increased ($p<0.01$) when compared to the expected number of 0.4 cases in this group. Similarly, three brain and CNS cancers were reported after a 15-year latency, while only 0.6 were expected ($p<0.05$). Respiratory system cancers numbered 11, while 5.7 were expected ($p<0.05$). Lymphatic and hematopoietic system cancer occurred in three workers exposed to vinyl chloride, which is suggestive of an increased incidence (1.7 expected) but is not statistically significant.

TABLE 4-1

Epidemiology Studies on Deaths due to Cancer Among Vinyl Chloride Workers

Size of Exposed Population	Size of Control Population	Sex	Level of Exposure	Duration of Exposure	Target Organ	Tumor Type	Number of Cases Observed*	Number of Cases Expected	Relative Risk (p value)	Reference
1287	U.S. death rates	M,F	NR	>5 years	liver and biliary	cancer	7	0.4	16.0 (p<0.01)	Waxweiler et al., 1976
					brain and CNS	cancer	3	0.6	5.0 (p<0.05)	
					lymphatic and hematopoietic	cancer	3	1.7	1.8 (NS)	
					respiratory system	cancer	11	5.7	1.9 (p<0.05)	
750	1969 Swedish population	M	periodically up to 15,000 ppm	>10 years	liver/pancreas	cancer	4	0.68	p<0.005	Bryen et al., 1976
				<1 to >10 years	brain	cancer	2	0.33	p<0.043	
				<1 to >10 years	lung	cancer	3	1.78	p<0.26	
7409	death rates for England and Wales	M	<25 to >200 ppm	6-20 years	liver	cancer	4	1.64	2.44	Fox and Collier, 1977
161	161	M	NR	NR	liver and biliary tract	cancer	8	0.7	11.0	Monson et al., 1974
					brain	cancer	5	1.2	4.2	
					lung	cancer	13	7.9	1.6	
					digestive	cancer	13	8.3	1.6	
					lymphatic and hematopoietic system	cancer	5	3.4	1.5	

*Incidence of tumors after 15-year latency

NS = Not significant; NR = Not reported

In a cohort study of 750 workers exposed to vinyl chloride for >10 years, Bryen et al. (1976) reported four liver/pancreatic cancers, two of which were confirmed liver angiosarcomas, compared to 0.68 cases expected ($p=0.005$). An additional case of hepatic hemangiosarcoma occurred after the data were compiled, and was therefore not included in the reported cases. Two cases of brain cancer were reported compared to 0.33 expected ($p<0.043$). The increased incidence of lung cancer (3 observed vs. 1.78 expected) was not statistically significant.

Fox and Collier (1977) examined the mortality of 7409 workers exposed to vinyl chloride in the production of polyvinyl chloride in eight factories. A total of four deaths due to liver cancer were reported, compared to 1.64 expected. Three of these cases occurred in a factory engaged in polyvinyl chloride production since 1944 (the longest period of those factories examined), while only 0.13 would have been expected ($p<0.01$) (Infante, 1981). It was noted, however, that 75% of this study cohort had been employed for <10 years, which does not allow for a sufficient latency period and therefore underestimates the observed risk of cancer.

Of 161 deaths among vinyl chloride workers, there were 8 liver and biliary cancers (0.7 expected; 11.0 risk ratio), 5 brain cancers (1.2 expected; 4.2 risk ratio), 13 lung cancers (7.9 expected; 1.6 risk ratio), 13 digestive tract cancers (8.3 expected; 1.6 risk ratio), and 5 lymphatic and hematopoietic cancers (3.4 expected; 1.5 risk ratio) (Monson et al., 1974). The authors did not report statistical comparisons of these data, but did note an excess frequency of liver, lung and brain cancers. It was also reported that the frequency of all cancers increased with length of exposure and latency (Monson et al., 1974).

4.2. BIOASSAYS

4.2.1. Oral. An oral study (Feron et al., 1981) in which vinyl chloride was given in the diet or by gavage was used by the U.S. EPA (1984) to derive a q_1* for oral exposure. In the dietary study groups of 60 male and 60 female 5-week-old Wistar rats were fed diets containing 10% PVC powder (PVC, containing not more than 0.3 ppm), which acted as a carrier for liquid VCM. A control group of 80 males and 80 females was given a diet containing PVC without added VCM. The VCM used in this study was >99.97% pure. Diets were prepared daily and offered for 6 hours each day. In addition, another control group (80 males and 80 females) was fed diets containing PVC without VCM *ad libitum* and an additional treatment group (60 males and 60 females) was given VCM in soya oil at 300 mg/kg bw/day. A vehicle control (soya oil) group was not used in this experiment. The feeding trials lasted for 135 weeks for males and 144 weeks for females. Gavage treatment was performed 5 days/week for 83 weeks.

Body weights and food consumptions were measured periodically throughout the study. Fecal VCM was subtracted from VCM intakes on the assumption that it represented VCM enclosed in PVC granules and not available to the body. Dietary levels of VCM of 0, 20, 60 and 200 ppm resulted in actual exposure of 0, 1.7, 5.0 and 14.1 mg VCM/kg bw/day. Complete histopathological examinations were performed on tissues and organs of 20 males and 20 females from the control (restricted feeding), high-dose diet and gavage groups at termination. In addition, all gross lesions and tumors were histopathologically examined as were selected tissues from 10 males and 10 females from these groups sacrificed at 26 and 52 weeks.

A statistically significant dose-related decrease in survival became evident in rats fed diets containing VCM at 80 weeks of treatment. Survival was also reduced in gavage-treated rats but statistical analyses were not performed because a vehicle control group had not been maintained. The U.S. EPA (1984) reported the incidences of liver and lung tumors by type and the q_1^* associated with each individual tumor in rats fed VCM in the diet. These data are presented in Tables 4-2 (males) and 4-3 (females). A dose-related increased incidence of hepatocellular carcinomas, and liver and lung angiosarcomas were noted in rats of both sexes. A high incidence of angiosarcoma of the lung (19/60 males, 23/60 females) was also noted in gavage-treated rats. A significantly increased incidence ($p<0.05$ at the two highest dose levels; Fisher Exact Test) of liver angiosarcomas was seen in Sprague-Dawley rats (40/sex/dose level) given vinyl chloride by gastric intubation (in olive oil) at levels of 0, 3.33, 16.65 or 50 mg/kg bw, 4-5 times/week, for 52 weeks (Maltoni, 1977a; Maltoni et al., 1975). Survival at 85 weeks after the beginning of treatment was 35 control, 39 low-dose, 32 mid-dose and 23 high-dose animals. After 120 weeks, the number and types of tumors reported were 1 Zymbal gland tumor in the control group; 1 intra-abdominal angiosarcoma in the low-dose group; 9 liver angiosarcomas, 2 Zymbal gland carcinomas, and 3 nephroblastomas in the mid-dose group; and 16 liver angiosarcomas, 2 nephroblastomas, 1 Zymbal gland carcinoma, 1 thymic angiosarcoma, and 1 intra-abdominal angiosarcoma in the high-dose group. The individual incidences for each sex were not segregated in the available summaries of this study (IARC, 1979; U.S. EPA, 1983b). The incidences of hepatic angiosarcoma and renal nephroblastoma are summarized in Table 4-4.

TABLE 4-2

Type and Incidence of Statistically Significant Treatment-Related Changes in the Liver and Lung of Male Wistar Rats Exposed to VCM in the Diet. Values of q_1^* and Concentration from Multistage Extrapolation Model Included[a]

	Treatment Group (mg/kg/day)				q_1^{*b}
	0	1.7	5.0	14.1	$(mg/kg/day)^{-1}$
Number of rats examined[c]	55	58	56	59	
Liver					
Neoplastic nodules	0	1	7	23	2.1×10^{-1}
Hepatocellular carcinomas	0	1	2	8	8.8×10^{-2}
Angiosarcomas	0	0	6	27	1.3×10^{-1}
Total liver tumors[d]	0	2	13	50	3.0×10^{-1}
Lung					
Angiosarcomas	0	0	4	19	1.1×10^{-1}
Total animals with tumors	0	2	17	58	2.9×10^{-1}

[a]Source: Adapted from Feron et al., 1981

[b]Human equivalent $q_1^* = q_1^*(a)(W_h/W_a)^{1/3}$ in $(mg/kg/day)^{-1}$

[c]Found dead or killed in extremis or terminally

[d]Sum of neoplastic nodules and liver angiosarcomas

TABLE 4-3

Type and Incidence of Statistically Significant Treatment-Related Changes in the Liver and Lung of Female Wistar Rats Exposed to VCM in the Diet. Values of q_1^* and Concentration from Multistage Extrapolation Model Included[a]

	Treatment Group (mg/kg/day)				q_1^{*b}
	0	1.7	5.0	14.1	$(mg/kg/day)^{-1}$
Number of rats examined[c]	57	58	59	57	
Liver					
Neoplastic nodules	2	26	39	44	1.3
Hepatocellular carcinomas	0	4	19	29	5.0×10^{-1}
Angiosarcomas	0	0	2	9	8.8×10^{-2}
Total liver tumors[d]	2	26	41	53	1.9
Lung					
Angiosarcomas	0	0	1	5	5.8×10^{-2}
Total animals with tumors	2	26	42	56	2.3

[a]Source: Adapted from Feron et al., 1981

[b]Human equivalent $q_1^* = q_1^*(a)(W_hW_a)^{1/3}$ in $(mg/kg/day)^{-1}$

[c]Found dead or killed in extremis or terminally

[d]Sum of neoplastic nodules and liver angiosarcomas

TABLE 4-4

Tumor Incidences in Sprague-Dawley Rats Dosed with Vinyl Chloride by Gavage[a]

Sex	Dose or Exposure[b] (mg/kg)	Duration of Treatment (weeks)	Duration of Study (weeks)	Purity of Compound	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence (p value)
NR	50	52	136	NR	olive oil	liver	angiosarcoma	16/80 ($p<0.05$)[c]
						kidney	nephroblastoma	2/80
NR	16.5	52	136	NR	olive oil	liver	angiosarcoma	9/80 ($p<0.05$)[c]
						kidney	nephroblastoma	3/80
M,F	0.0	52	136	NA	olive oil only	liver	angiosarcoma	0/150
						kidney	nephroblastoma	0/150

[a]Source: Maltoni, 1977b

[b]Exposure to vinyl chloride by gavage was once daily in olive oil 4-5 days/week for 52 weeks

[c]Fisher exact test was performed by Syracuse Research Corporation

NA = Not applicable; NR = Not reported

4.2.2. *Inhalation. There are numerous inhalation studies on the carcinogenicity* of vinyl chloride in experimental animals. Inhalation exposures to vinyl chloride have resulted in increased incidences of various tumors, including pulmonary adenomas and adenocarcinomas, angiosarcomas of the liver and other sites, lymphomas, mammary carcinomas, and neuroblastomas of the brain, in mice, rats and hamsters (Wagoner, 1983). Inhalation exposure to vinyl chloride at concentrations as low as 10 ppm have resulted in hepatic and extrahepatic angiosarcomas, whereas mammary carcinomas are produced at even lower concentrations (e.g., 1 or 5 ppm) (Wagoner, 1983). Due to the limitations of this project, only the most substantial studies will be reviewed and used as a basis for evaluating carcinogenic risk associated with inhalation exposure to vinyl chloride. The reader is referred to the summaries by U.S. EPA (1980a, 1982, 1983b) and IARC (1979).

Maltoni and Lefemine (1974a,b, 1975) investigated the carcinogenic effects of inhaled vinyl chloride in rats exposed to concentrations ranging from 50-10,000 ppm for 5 days/week, for 52 weeks. The animals were observed for tumor development for their lifespan (length of experiment equal to 135 weeks). The total tumor incidences after 135 weeks, reported by U.S. EPA (1980a) as the basis for deriving a human cancer based criterion for vinyl chloride, were 6/58 controls, 10/59 at the 50 ppm level, 16/59 at the 250 ppm level, 22/59 at the 500 ppm level, 32/59 at the 2500 ppm level, 31/60 at the 6000 ppm level, and 38/61 at the 10,000 ppm level. Differential responses between the sexes were not reported. The tumor types included hepatic angiosarcomas, renal nephroblastomas, Zymbal gland carcinomas, and others unspecified. These tumor incidences are summarized in Table 4-5.

TABLE 4-5

Incidence of Tumors in Sprague-Dawley Rats Exposed 4 Hours/Day, 5 Days/Week, for 52 Weeks by Inhalation to Various Concentrations of Vinyl Chloride: Results after 135 Weeks*

Concentration (ppm)	Number of Animals		Liver		Kidney		Zymbal Gland		Other	Total Number of Rats with One or More Tumors
	Total	Corrected	Angio-sarcomas	Average Latency (weeks)	Nephro-blastomas	Average latency (weeks)	Carcinomas	Average Latency (weeks)		
10,000	69	61	9	64	5	59	16	50	25	38
6,000	72	60	13	70	4	65	7	62	19	31
2,500	74	59	13	78	6	74	2	33	18	32
500	67	59	7	81	4	83	4	79	11	22
250	67	59	4	79	6	80	0	0	9	16
50	64	59	1	135	1	135	0	0	12	10
No treatment	68	58	0	0	0	0	0	0	10	6

*Source: Maltoni and Lefemine, 1975

Viola et al. (1971) reported an increased incidence of skin carcinomas, lung carcinomas and osteochondromas in Wistar rats exposed to 30,000 ppm of vinyl chloride by inhalation. Since then, studies by Maltoni (1977b), Maltoni et al. (1981), Lee et al. (1978) and Hong et al. (1981) have also provided evidence of the carcinogenicity of vinyl chloride in experimental animals. These five studies are summarized in Tables 4-6 through 4-10.

Maltoni (1977b) reported an increased incidence of hepatic angiosarcoma and renal nephroblastoma in Sprague-Dawley rats exposed by inhalation. Kidney nephroblastomas were seen in animals exposed to 6000 or 10,000 ppm of vinyl chloride, whereas an increased incidence of liver angiosarcoma was reported in groups exposed to concentrations as low as 100 ppm. More recently, Maltoni et al. (1981) reported kidney nephroblastomas in groups of rats exposed by inhalation to 25 ppm of vinyl chloride, while control groups had none. Liver angiosarcomas were evident in rats exposed to 100 ppm of vinyl chloride by inhalation. Similar tumors were not seen in rats exposed to 0, 1 or 5 ppm of vinyl chloride. For groups of Swiss mice exposed by inhalation to 50, 250, 500, 2500, 6000 or 10,000 ppm of vinyl chloride, Maltoni et al. (1981) reported a dose-related incidence of liver angiosarcomas and lung tumors. In Golden hamsters exposed at the same levels, papillomas and acanthomas of the forestomach were produced by vinyl chloride exposure.

In groups of 36 male and 36 female CD rats, lung and liver hemangiosarcomas were produced in groups of animals exposed by inhalation to 250 or 1000 ppm of vinyl chloride (Lee et al., 1978). This study indicated that females of this strain were more susceptible to the carcinogenic effect of vinyl chloride. Rats treated with 0 or 50 ppm of vinyl chloride did not

TABLE 4-6

Tumor Incidences in Male Wistar (Ar/IRE) Rats Exposed to 30,000 ppm of Vinyl Chloride by Inhalation[a]

Dose or Exposure[b] (ppm)	Duration of Treatment	Duration of Study	Purity of Compound	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence
30,000	12 months	>12 months	99%	vapor/air	skin	epidermoid carcinoma	15/26
					lung	carcinoma	6/26
					bone	osteochondroma	5/26
0	NA	>12 months	NA	air only	skin	epidermoid carcinoma	0/25
					lung	carcinoma	0/25
					bone	osteochondroma	0/25

[a]Source: Viola et al., 1971

[b]Exposure was for 4 hours/day, 5 days/week for 12 months.

NA = Not applicable

TABLE 4-7

Tumor Incidences in Sprague-Dawley Rats Exposed to 100-10,000 ppm of Vinyl Chloride[a]

Exposure Route	Dose or Exposure[b] (ppm)	Duration of Treatment (weeks)	Duration of Study (weeks)	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence
Inhalation	10,000	52	155	vapor/air	liver kidney	angiosarcoma nephroblastoma	9/60 5/60
Inhalation	6,000	52	155	vapor/air	liver kidney	angiosarcoma nephroblastoma	13/60 4/60
Inhalation	200	52	143	vapor/air	liver	angiosarcoma	12/120
Inhalation	150	52	143	vapor/air	liver	angiosarcoma	5/120
Inhalation	100	52	143	vapor/air	liver	angiosarcoma	1/120
NA	0	52	143-155	air only	liver kidney	angiosarcoma nephroblastoma	0/500 0/120

[a]Source: Maltoni, 1977b

[b]Exposure to vinyl chloride by inhalation was for 4 hours/day, 5 days/week for 52 weeks

NA = Not applicable; NR = Not reported

TABLE 4-8

Tumor Incidences in Sprague-Dawley Rats, Swiss Mice and Syrian Golden Hamsters Exposed to Various Concentrations of Vinyl Chloride by Inhalation[a,b]

Sex	Dose or Exposure[c] (ppm)	Duration of Treatment (weeks)	Duration of Study (weeks)	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence
				RATS			
M,F	30,000	52	60	air/vapor	liver kidney	angiosarcoma nephroblastoma	18/60 NR
M,F	10,000	52	135	air/vapor	liver kidney	angiosarcoma nephroblastoma	7/60 5/60
M,F	6,000	52	135	air/vapor	liver kidney	angiosarcoma nephroblastoma	13/59 5/59
M,F	2,500	52	135	air/vapor	liver kidney	angiosarcoma nephroblastoma	13/60 6/60
M,F	500	52	135	air/vapor	liver kidney	angiosarcoma nephroblastoma	6/60 6/60
M,F	250	52	135	air/vapor	liver kidney	angiosarcoma nephroblastoma	3/59 5/59
M,F	200	52	143	air/vapor	liver kidney	angiosarcoma nephroblastoma	12/120 7/120
M,F	150	52	143	air/vapor	liver kidney	angiosarcoma nephroblastoma	6/119 11/119
M,F	100	52	143	air/vapor	liver kidney	angiosarcoma nephroblastoma	1/120 10/120
M,F	50	52	135	air/vapor	liver kidney	angiosarcoma nephroblastoma	1/60 1/60
M,F	25	52	147	air/vapor	liver kidney	angiosarcoma nephroblastoma	5/120 1/120

TABLE 4-8 (cont.)

Sex	Dose or Exposure[c] (ppm)	Duration of Treatment (weeks)	Duration of Study (weeks)	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence
				RATS (cont.)			
M,F	10	52	147	air/vapor	liver kidney	angiosarcoma nephroblastoma	1/119 0/119
M,F	5	52	147	air/vapor	liver kidney	angiosarcoma nephroblastoma	0/119 0/119
M,F	1	52	147	air/vapor	liver kidney	angiosarcoma nephroblastoma	0/118 0/118
M,F	0	NA	135-147	air only	liver kidney	angiosarcoma nephroblastoma	0/363 0/363
				MICE			
M,F	10,000	30	81	air/vapor	liver lung	angiosarcoma tumor	10/56 46/56
M,F	6,000	30	81	air/vapor	liver lung	angiosarcoma tumor	13/60 47/60
M,F	2,500	30	81	air/vapor	liver lung	angiosarcoma tumor	16/59 40/59
M,F	500	30	81	air/vapor	liver lung	angiosarcoma tumor	14/60 50/60
M,F	250	30	81	air/vapor	liver lung	angiosarcoma tumor	18/60 41/60
M,F	50	30	81	air/vapor	liver lung	angiosarcoma tumor	1/60 6/60
M,F	0	NA	81	air only	liver lung	angiosarcoma tumor	0/150 15/150

TABLE 4-8 (cont.)

Sex	Dose or Exposure[c] (ppm)	Duration of Treatment (weeks)	Duration of Study (weeks)	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence
				HAMSTERS			
M,F	10,000	30	109	air/vapor	forestomach	papilloma/acanthoma	10/30
M,F	6,000	30	109	air/vapor	forestomach	papilloma/acanthoma	10/30
M,F	2,500	30	109	air/vapor	forestomach	papilloma/acanthoma	17/30
M,F	500	30	109	air/vapor	forestomach	papilloma/acanthoma	9/30
M,F	250	30	109	air/vapor	forestomach	papilloma/acanthoma	4/30
M,F	50	30	109	air/vapor	forestomach	papilloma/acanthoma	3/30
M,F	0	NA	109	air only	forestomach	papilloma/acanthoma	3/60

[a]Source: Maltoni et al., 1981

[b]Purity of compound was >99.9%

[c]Exposure was for 4 hours/day, 5 days/week

NA = Not applicable; NR = Not reported

TABLE 4-9

Tumor Incidences in CD Rats and CD-1 Mice Exposed to 50-1000 ppm of Vinyl Chloride by Inhalation[a]

Sex	Dose or Exposure[b] (ppm)	Duration of Treatment (months)	Duration of Study (months)	Purity of Compound	Vehicle or Physical State	Target Organ	Tumor Type[b]	Tumor Incidence (p value)
				RATS				
M	50	12	12	99.8%	vapor/air	liver	hemangiosarcoma	0/36
						lung	hemangiosarcoma	0/36
F	50	12	12	99.8%	vapor/air	liver	hemangiosarcoma	0/36
						lung	hemangiosarcoma	0/36
M	250	12	12	99.8%	vapor/air	liver	hemangiosarcoma	2/36
						lung	hemangiosarcoma	0/36
F	250	12	12	99.8%	vapor/air	liver	hemangiosarcoma	10/34 ($p<0.05$)
						lung	hemangiosarcoma	3/34
M	1000	12	12	99.8%	vapor/air	liver	hemangiosarcoma	6/34
						lung	hemangiosarcoma	4/34
F	1000	12	12	99.8%	vapor/air	liver	hemangiosarcoma	15/36 ($p<0.05$)
						lung	hemangiosarcoma	9/36
M	0	NA	12	NA	air only	liver	hemangiosarcoma	0/35
						lung	hemangiosarcoma	0/35
F	0	NA	12	NA	air only	liver	hemangiosarcoma	0/35
						lung	hemangiosarcoma	0/35

TABLE 4-9 (cont.)

Sex	Dose or Exposure[b] (ppm)	Duration of Treatment (months)	Duration of Study (months)	Purity of Compound	Vehicle or Physical State	Target Organ	Tumor Type[b]	Tumor Incidence (p value)
				MICE				
M	0	NA	12	NA	air only	respiratory tract	bronchioloalveolar adenoma	1/26
						liver	hemangiosarcoma	0/26
F	0	NA	12	NA	air only	respiratory tract	bronchioloalveolar adenoma	0/36
						liver	hemangiosarcoma	0/36
M	50	12	12	99.8%	vapor/air	respiratory tract	bronchioloalveolar adenoma	8/29
						liver	hemangiosarcoma	3/29
F	50	12	12	99.8%	vapor/air	respiratory tract	bronchioloalveolar adenoma	4/34
						liver	hemangiosarcoma	0/34
M	250	12	12	99.8%	vapor/air	respiratory tract	bronchioloalveolar adenoma	10/29
						liver	hemangiosarcoma	7/29 ($p<0.05$)
F	250	12	12	99.8%	vapor/air	respiratory tract	bronchioloalveolar adenoma	12/34
						liver	hemangiosarcoma	16/34 ($p<0.05$)
M	1000	12	12	99.8%	vapor/air	respiratory tract	bronchioloalveolar adenoma	22/33
						liver	hemangiosarcoma	13/33 ($p<0.05$)
F	1000	12	12	99.8%	vapor/air	respiratory tract	bronchioloalveolar adenoma	26/36
						liver	hemangiosarcoma	18/36 ($p<0.05$)

[a] Source: Lee et al., 1978

[b] Exposure was for 6 hours/day, 5 days/week

NA = Not applicable

TABLE 4-10

Tumor Incidences in CD Rats and CD-1 Mice Exposed to Various Concentrations of Vinyl Chloride by Inhalation[a]

Sex	Dose or Exposure[b] (ppm)	Duration of Treatment (months)	Duration of Study (months)	Purity of Compound	Vehicle or Physical State	Target Organ	Tumor Type[c]	Tumor Incidence
				RATS				
M,F	50	6 or 10[d]	18 or 22[d]	99.8%	air/vapor	liver	hepatocellular carcinoma	0/66
							hemangiosarcoma	0/66
						lung	bronchioloalveolar tumor	0/66
							hemangiosarcoma	0/66
M,F	250	6 or 10[d]	18 or 22[d]	99.8%	air/vapor	liver	hepatocellular carcinoma	2/68
							hemangiosarcoma	5/68
						lung	bronchioloalveolar tumor	2/68
							hemangiosarcoma	2/68
M,F	1000	6 or 10[d]	18 or 22[d]	99.8%	air/vapor	liver	hepatocellular carcinoma	7/72
							hemangiosarcoma	14/72
						lung	bronchioloalveolar tumor	4/72
							hemangiosarcoma	7/72
M,F	0	6 or 10[d]	18 or 22[d]	99.8%	air/vapor	liver	hepatocellular carcinoma	1/72
							hemangiosarcoma	0/72
						lung	bronchioloalveolar tumor	0/72
							hemangiosarcoma	0/72
				MICE				
M,F	50	1	13	99.8%	air/vapor	lung	bronchioloalveolar tumor	3/32
						liver	hemangiosarcoma	1/32
M,F	250	1	13	99.8%	air/vapor	lung	bronchioloalveolar tumor	19/32
						liver	hemangiosarcoma	0/32
M,F	1000	1	13	99.8%	air/vapor	lung	bronchioloalveolar tumor	20/32
						liver	hemangiosarcoma	0/32

TABLE 4-10 (cont.)

Sex	Dose or Exposure[b] (ppm)	Duration of Treatment (months)	Duration of Study (months)	Purity of Compound	Vehicle or Physical State	Target Organ	Tumor Type[c]	Tumor Incidence
				MICE (cont.)				
M,F	0	1	13	99.8%	air/vapor	lung	bronchioloalveolar tumor	3/32
						liver	hemangiosarcoma	0/32
M,F	50	3	15	99.8%	air/vapor	lung	bronchioloalveolar tumor	12/32
						liver	hemangiosarcoma	0/32
M,F	250	3	15	99.8%	air/vapor	lung	bronchioloalveolar tumor	21/32
						liver	hemangiosarcoma	4/32
M,F	1000	3	15	99.8%	air/vapor	lung	bronchioloalveolar tumor	5/20
						liver	hemangiosarcoma	16/20
M,F	0	3	15	99.8%	air/vapor	lung	bronchioloalveolar tumor	2/32
						liver	hemangiosarcoma	0/32
M,F	50	6	18	99.8%	air/vapor	lung	bronchioloalveolar tumor	3/16
						liver	hemangiosarcoma	1/16
M,F	250	6	18	99.8%	air/vapor	lung	bronchioloalveolar tumor	12/20
						liver	hemangiosarcoma	9/20
M,F	1000	6	18	99.8%	air/vapor	lung	bronchioloalveolar tumor	14/24
						liver	hemangiosarcoma	13/24
M,F	0	6	18	99.8%	air/vapor	lung	bronchioloalveolar tumor	11/56
						liver	hemangiosarcoma	1/56

[a]Source: Hong et al., 1981

[b]Exposure for 6 hours/day, 5 days/week

[c]Showed dose-related response; significant at $p<0.05$

[d]Duration of exposure was for 6 or 10 months, followed by a 12-month latency period. The results presented are for the combined treatment-duration group.

develop similar tumors. Lee et al. (1978) also reported an increased incidence of bronchioalveolar adenoma and hepatic hemangiosarcomas in male and female CD-1 mice exposed to 50, 250 or 1000 ppm of vinyl chloride by inhalation for 6 hours/day, 5 days/week.

In a study examining the carcinogenic effect of vinyl chloride at various doses (50, 250 or 1000 ppm) by inhalation for various durations of treatment (6 or 10 months treatment period for rats; 1, 3 or 6 months treatment period for mice), Hong et al. (1981) reported elevated numbers of lung and liver hemangiosarcomas, hepatocellular carcinomas and bronchioloalveolar tumors in rats treated with 250 ppm of vinyl chloride for 6 or 10 months duration. All four tumor types showed a significant dose-related response in rats. In mice, only hemangiosarcomas showed a dose-related response. One month of exposure to 250 or 1000 ppm of vinyl chloride for 6 hours/day, 5 days/week, followed by a 12-month latency period, was sufficient to produce an increased incidence of bronchioloalveolar tumors in mice.

4.3. OTHER RELEVANT DATA

The mutagenicity of vinyl chloride has been reviewed by IARC (1979), U.S. EPA (1980a), Bartsch and Montesano (1975), Bartsch et al. (1976) and Fishbein (1976). Vapors of vinyl chloride induced reverse mutations in Salmonella typhimurium in the presence of a 9000 x g supernatant from rat liver (Andrews et al., 1976; Bartsch et al., 1975; Garro et al., 1976; Malaveille et al., 1975; McCann et al., 1975; Rannug et al., 1974) from mouse liver (Bartsch et al., 1975; Garro et al., 1976; Malaveille et al., 1975), and from human liver biopsy specimens (Bartsch et al., 1975, 1979; Malaveille et al., 1975). Vinyl chloride vapors induced mutations in the S. typhimurium assay without metabolic activation, but the mutagenic response was much higher with metabolic activation (Andrews et al., 1976; Bartsch et al., 1975; McCann et al., 1975).

When tested in aqueous or methanolic solution, vinyl chloride was negative in the _S. typhimurium_ test system (Bartsch et al., 1975; Rannug et al., 1974) but induced reverse mutations in _Escherichia coli_ K12 (Greim et al., 1975), forward mutations in _Schizosaccharomyces pombe_ and mitotic gene conversions in _Saccharomyces cerevisiae_ in the presence of mammalian metabolic activation (Loprieno et al., 1976, 1977).

Both vapors and an ethanol solution of vinyl chloride were negative in a mutagenicity assay with _Neurospora crassa_, regardless of whether metabolic activation was present or not (Drozdowicz and Huang, 1977). Forward mutations were induced in V79 Chinese hamster cells by vinyl chloride in the presence of a mammalian metabolic activation system (Drevon et al., 1977). Vinyl chloride vapors induced a significantly increased frequency of recessive lethals in _Drosophila melanogaster_ (Magnusson and Ramel, 1976; Verburgt and Vogel, 1977) but not dominant lethals, translocations or sex-chromosome loss (Verburgt and Vogel, 1977). No dominant lethal mutations were observed in male CD-1 mice exposed to various levels of vinyl chloride by inhalation (Anderson et al., 1976, 1977).

4.4. WEIGHT OF EVIDENCE

Vinyl chloride has been shown to be a carcinogen in rats, mice and hamsters. It produces a high incidence of liver, kidney, lung and brain tumors in a dose-related response when administered by oral or inhalation routes. Similar carcinogenic effects have been reported in workers exposed to vinyl chloride. The predominant target organs are the liver, brain, lung and lympho-hematopoietic system, but a general non-specific carcinogenic effect has been suggested. IARC (1982) concluded that there is sufficient evidence for carcinogenicity in both humans and experimental animals.

Applying the criteria for evaluating the overall weight of evidence of carcinogenicity to humans proposed by the Carcinogen Assessment Group of the U.S. EPA (Federal Register, 1984) vinyl chloride is most appropriately classified as a chemical in Group A - Human Carcinogen.

5. REGULATORY STANDARDS AND CRITERIA

ACGIH (1983) has established a TLV-TWA of 5 ppm (10 mg/m³) of vinyl chloride. The standards adopted by OSHA in 1981 are 1 ppm (2.6 mg/m³) of vinyl chloride as an 8-hour TWA and 5 ppm (13 mg/m³) of vinyl chloride as a ceiling concentration limit average over any period of $\leq$15 minutes (Code of Federal Regulations, 1981). Similar hygienic standards for occupational exposures in foreign countries exist; these are summarized in Table 5-1.

In the United States, vinyl chloride has been used in limited quantities as an aerosol propellant, but in 1974 it was banned from use in pesticide aerosol products (U.S. EPA, 1974), in self-pressurized household containers, and as an ingredient of drug and cosmetic products (U.S. Consumer Product Safety Commission, 1974a,b).

TABLE 5-1

Hygienic Standards for Occupational Exposure to Vinyl Chloride in Foreign Countries*

Country	Concentration (ppm)	Standard
Canada	10	8-hour TWA
	25	15-minute ceiling
Finland	5	8-hour TWA
	10	10-minute ceiling
Italy	50	8-hour TWA
The Netherlands	10	8-hour TWA
Norway	1	8-hour TWA
	5	15-minute ceiling
Sweden	1	8-hour TWA
	5	15-minute ceiling
USSR	12	NR
France		
existing factories	5	1-week TWA
	15	ceiling
new factories	1	1-week TWA
	5	ceiling
Denmark	1	8-hour TWA
Belgium	5	1-week TWA
	15	ceiling
Federal Republic of Germany		
existing factories	5	1-week TWA
	15	1-hour ceiling
new factories	2	1-week TWA
	15	1-hour ceiling
United Kingdom	10	8-hour TWA
	30	ceiling (maximum)
Switzerland	10	1-week TWA

*Sources: IARC, 1979; Bertram, 1977; Thomas, 1977

NR = Not reported

6. RISK ASSESSMENT

6.1. ACCEPTABLE INTAKE SUBCHRONIC (AIS)

Vinyl chloride is a chemical that is a known human and animal carcinogen and data are sufficient for calculation of a q_1*. It is inappropriate, therefore, to calculate an AIS for vinyl chloride.

6.2. ACCEPTABLE INTAKE CHRONIC (AIC)

Vinyl chloride is a chemical that is a known human and animal carcinogen and data are sufficient for calculation of a q_1*. It is inappropriate, therefore, to calculate an AIC for vinyl chloride.

6.3. CARCINOGENIC POTENCY (q_1*)

6.3.1. Oral. A dose-related increased incidence of neoplastic nodules of the liver, hepatocellular carcinomas and angiosarcomas of the liver and the lung were observed in both male and female rats fed diets containing vinyl chloride for 135 weeks (males) or 144 weeks (females) (Feron et al., 1981). The incidences of each tumor type and the associated human q_1* were presented in Tables 4-2 and 4-3 for males and females, respectively. The q_1* values ranged from 8.8×10^{-2} to 1.3 $(mg/kg/day)^{-1}$ for individual tumor types. A q_1* was also calculated for rats of each sex based on the incidence of total animals with tumors. The incidence of hepatocellular carcinoma was not included in these tallies because it was assumed that rats having hepatocellular carcinoma also bore neoplastic nodules, since neoplastic modules are considered to be preneoplastic forerunners of hepatocellular carcinomas. Furthermore, the total number of animals bearing tumors in the high-dose groups was arbitrarily reduced to one less than the total number of animals examined, so that the resulting data would fit the linear non-threshold model adopted by the U.S. EPA (1980b) for estimation of carcinogenic potency. The human q_1*s resulting from this manipulation were

2.9×10^{-1} (mg/kg/day)$^{-1}$ (males) and 2.3 (mg/kg/day)$^{-1}$ (females). The q_1^* of 2.3 (mg/kg/day)$^{-1}$ associated with total tumors in female rats was chosen by the U.S. EPA (1984) as most conservatively representing the carcinogenic potency of vinyl chloride.

6.3.2. Inhalation. The U.S. EPA (1980a) derived a q_1^* for humans for oral exposure from the incidence of total tumors in rats exposed to vinyl chloride by inhalation (Maltoni and Lefemine, 1975). This q_1^* has been superseded by a q_1^* for oral exposure based on the incidence of total tumors in female rats fed diets containing vinyl chloride (see Section 6.3.1.). The tumor incidence data in rats exposed by inhalation in the Maltoni and Lefemine (1975) study may more appropriately be used to derive a q_1^* for humans exposed by inhalation.

Using the linear non-threshold model adopted by the U.S. EPA (1980b) and the data from the Maltoni and Lefemine (1975) study summarized in Appendix B, a human q_1^* of 2.5×10^{-2} (mg/kg/day)$^{-1}$ is calculated. This slope value, in transformed units, is the same as that developed in U.S. EPA (1980a) without inclusion of the empirically derived factor to estimate oral exposure from inhalation data. U.S. EPA (1980a) estimated a unit risk of 6.80×10^{-3} (ppm)$^{-1}$ based on the rat inhalation data. Assuming that rats breathe 0.223 m^3/day (U.S. EPA, 1980b) and weigh 0.35 kg, this unit risk can be converted to an animal q_1^* of 4.2×10^{-3} (mg/kg/day)$^{-1}$. Estimation of an equivalent human q_1^* was accomplished by using a surface area approximation: $(70/0.35)^{1/3}$, i.e., 4.2×10^{-3} (mg/kg/day)$^{-1}$ x $(70/0.35)^{1/3}$ = 2.5×10^{-2} (mg/kg/day)$^{-1}$ (U.S. EPA, 1980b).

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APPENDIX A

Summary Table for Vinyl Chloride

Carcinogenic Potency	Species	Experimental Dose/Exposure	Effect	q_1^* $(mg/kg/day)^{-1}$	Reference
Inhalation	rats	50-10,000 ppm	total tumors	2.5×10^{-2}	Maltoni and Lefemine, 1975
Oral	rats	16.65 or 50 mg/kg bw	angiosarcomas	2.3	Feron et al., 1981; U.S. EPA, 1984

APPENDIX B

Cancer Data Sheet for Derivation of q_1*

Compound: Vinyl chloride

Reference: Maltoni and Lefemine, 1975

Species, strain, sex: rats, Sprague-Dawley, male and female

Body weight: 0.35 kg (assumed)

Length of exposure (le) = 52 weeks, 4 hours/day, 5 days/week

Length of experiment (Le) = 104 weeks

Lifespan of animal (L) = 104 weeks

Tumor site and type: total tumors

Route, vehicle: inhalation

Experimental Doses or Exposures (ppm)	(mg/m³)	Input: Transformed Dose† (mg/kg/day)	Input: Incidence No. Responding/No. Tested (or Examined)
0	0	0	6/58
50	127.8	4.9	10/59
250	639.1	23.9	16/59
500	1,278.1	47.8	22/59
2,500	6,390.6	239.1	32/59
6000	15,337.4	573.8	31/60
10,000	25,562.4	956.4	38/61

†Assumes rats breathe 0.223 m³/day, reflects time-weighted average exposure incorporating factors of 4 hours/24 hours, 5 days/7 days and 52 weeks/104 weeks

Unadjusted q_1* from study = 4.2×10^{-3} $(mg/kg/day)^{-1}$

Human q_1* = 2.5×10^{-2} $(mg/kg/day)^{-1}$

C-8 (j) TOTAL XYLENES

The attached Integrated Risk Information System (IRIS) printout (March 1990) is provided as a technical summary.

Xylenes; CASRN 1330-20-7 (07/01/89)

Health risk assessment information on a chemical is included in IRIS only after a comprehensive review of chronic toxicity data by work groups composed of U.S. EPA scientists from several Program Offices. The summaries presented in Sections I and II represent a consensus reached in the review process. The other sections contain U.S. EPA information which is specific to a particular EPA program and has been subject to review procedures prescribed by that Program Office. The regulatory actions in Section IV may not be based on the most current risk assessment, or may be based on a current, but unreviewed, risk assessment, and may take into account factors other than health effects (e.g., treatment technology). When considering the use of regulatory action data for a particular situation, note the date of the regulatory action, the date of the most recent risk assessment relating to that action, and whether technological factors were considered. Background information and explanations of the methods used to derive the values given in IRIS are provided in the five Background Documents in Service Code 5, which correspond to Sections I through V of the chemical files.

STATUS OF DATA FOR Xylenes

File On-Line 09/30/87

Category (section)	Status	Last Revised
Oral RfD Assessment (I.A.)	on-line	09/30/87
Inhalation RfD Assessment (I.B.)	pending	
Carcinogenicity Assessment (II.)	on-line	09/26/88
Drinking Water Health Advisories (III.A.)	no data	
U.S. EPA Regulatory Actions (IV.)	on-line	03/01/88

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_I. CHRONIC HEALTH HAZARD ASSESSMENT FOR NONCARCINOGENIC EFFECTS

Substance Name -- Xylenes
CASRN -- 1330-20-7
Last Revised -- 09/30/87

The Reference Dose (RfD) is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis, but may not exist for other toxic effects such as carcinogenicity. In general, the RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Please refer to Background Document 1 in Service Code 5 for an elaboration of these concepts. RfDs can also be derived for the noncarcinogenic health effects of compounds which are also carcinogens. Therefore, it is essential to refer to other sources of information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file when a review of that evaluation is completed.

<<< Xylenes >>>

__I.A. REFERENCE DOSE FOR CHRONIC ORAL EXPOSURE (RfDo)

___I.A.1. ORAL RfD SUMMARY

Critical Effect	Experimental Doses*	UF	MF	RfD
Hyperactivity, decreased body weight and increased mortality (males)	NOAEL: 250 mg/kg/day (converted to 179 mg/kg/day)	100	1	2E+0 mg/kg/day
Chronic Rat Gavage Study	FEL: 500 mg/kg/day (converted to 357 mg/kg/day)			
NTP, 1986				

*Conversion Factors: Dose adjusted for gavage schedule (5 days/week).

<<< Xylenes >>>

___I.A.2. PRINCIPAL AND SUPPORTING STUDIES (ORAL RfD)

NTP (National Toxicology Program). 1986. NTP Technical Report on the Toxicology and Carcinogenesis of Xylenes (mixed) (60.2% m-xylene, 13,6% p-xylene, 17.0 ethylbenzene and 9.1% O-xylene) (CAS No. 1330-20-7) in F344/N rats and B6C3F1 mice (gavage studies). U.S. DHHS, PHS, NIH, NTP, Research Triangle Park, NC. NTP TR 327, NIH Publ. No. 86-2583.

Groups of 50 male and 50 female Fischer 344 rats and 50 male and 50 female B6C3F1 mice were given gavage doses of 0, 250, or 500 mg/kg/day (rats) and 0, 500, or 1000 mg/kg/day (mice) for 5 days/week for 103 weeks. The animals were observed for clinical signs of toxicity, body weight gain, and mortality. All animals that died or were killed at sacrifice were given gross necropsy and comprehensive histologic examinations. There was a dose-related increased mortality in male rats, and the increase was significantly greater in the high-dose group compared with controls. Although increased mortality was observed at 250 mg/kg/day, the increase was not significant. Although many of the early deaths were caused by gavage error, NTP (1986) did not rule out the possibility that the rats were resisting gavage dosing because of the behavioral effects of xylene. Mice given the high dose exhibited hyperactivity, a manifestation of CNS toxicity. There were no compound-related histopathologic lesions in any of the treated rats or mice. Therefore, the high dose is a FEL and the low dose a NOAEL.

<<< Xylenes >>>

___I.A.3. UNCERTAINTY AND MODIFYING FACTORS (ORAL RfD)

UF = 100. An uncertainty factor of 100 was chosen: 10 for species-to-species extrapolation and 10 to protect sensitive individuals.

MF = 1.

___I.A.4. ADDITIONAL COMMENTS (ORAL RfD)

U.S. EPA (1984) reported an RfD of 0.01 mg/kg/day, based on a rat dietary NOAEL of 200 ppm or 10 mg/kg/day as defined by Bowers et al. (1982) in a 6-month study. This NOAEL was divided by an uncertainty factor of 1000. U.S. EPA (1985, 1986) noted that this study used aged rats, loss of xylene from volatilization was not controlled, only one exposure level was used, and histopathologic examination was incomplete. An RfD of 4.31 mg/day (about 0.06 mg/kg/day) based on an inhalation study (Jenkins et al., 1970) using rats, guinea pigs, monkeys, and dogs exposed to o-xylene at 3358 mg/cu.m, 8 hours/day, 5 days/ week for 6 weeks or at 337 mg/cu.m continuously for 90 days was derived by U.S. EPA (1985). Deaths in rats and monkeys, and tremors in dogs occurred at the highest dose, whereas no effects were observed in the 337 mg/cu.m continuous exposure group. The RfD based on the NTP (1986) study is preferable because it is based on a chronic exposure in two species by a relevant route of administration, and comprehensive histology was performed. Xylene is fetotoxic and teratogenic in mice at high oral doses (Nawrot and Staples, 1981; Marks et al., 1982), but the RfD as calculated should be protective of these effects.

<<< Xylenes >>>

___I.A.5. CONFIDENCE IN THE ORAL RfD

Study: Medium
Data Base: Medium
RfD: Medium

The NTP (1986) study was given a medium confidence level because it was a well-designed study in which adequately sized groups of two species were tested over a substantial portion of their lifespan, comprehensive histology was performed, and a NOAEL was defined; but clinical chemistries, blood enzymes, and urinalysis were not performed. The data base was given a medium confidence level because, although supporting data exist for mice and teratogenicity and fetotoxicity data are available with positive results at high oral doses, a LOAEL for chronic oral exposure has not been defined. Medium confidence in the RfD follows.

<<< Xylenes >>>

___I.A.6. EPA DOCUMENTATION AND REVIEW OF THE ORAL RfD

U.S. EPA. 1986. Health and Environmental Effects Profile for Xylenes (o-, m-, p-). Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH and the Environmental Criteria and Assessment Office, Research Triangle Park, NC for the Office of Solid Waste and Emergency Response and the Office of Air Quality Planning and Standards, Office of Air and Radiation, Washington, DC.

Limited peer review and extensive agency-wide review, 1986.

U.S. EPA. 1985. Drinking Water Criteria Document For Xylenes. Prepared by Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Drinking Water, Washington, DC.

Extensive peer review agency-wide review.

U.S. EPA. 1984. Health Effects Assessment for Xylene. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Emergency and Remedial Response, Washington, DC.

ECAO internal review and limited agency review.

Agency RfD Work Group Review: 12/05/85, 03/19/87

Verification Date: 03/19/87

___I.A.7. EPA CONTACTS (ORAL RfD)

Harlal Choudhury / ORD -- (513)569-7536 / FTS 684-7536

Christopher T. DeRosa / ORD -- (513)569-7534 / FTS 684-7534

------<<< Xylenes >>>------

__I.B. REFERENCE DOSE FOR CHRONIC INHALATION EXPOSURE (RfDi)

A risk assessment for this chemical is under review by an EPA work group.

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_II. CARCINOGENICITY ASSESSMENT FOR LIFETIME EXPOSURE

Substance Name -- Xylenes
CASRN -- 1330-20-7
Last Revised -- 09/26/88

Section II provides information on three aspects of the carcinogenic risk assessment for the agent in question; the U.S. EPA classification, and quantitative estimates of risk from oral exposure and from inhalation exposure. The classification reflects a weight-of-evidence judgment of the likelihood that the agent is a human carcinogen. The quantitative risk estimates are presented in three ways. The slope factor is the result of application of a low-dose extrapolation procedure and is presented as the risk per mg/kg/day. The unit risk is the quantitative estimate in terms of either risk per ug/L drinking water or risk per ug/cu.m air breathed. The third form in which risk is presented is a drinking water or air concentration providing cancer risks of 1 in 10,000, 1 in 100,000 or 1 in 1,000,000. Background Document 2 (Service Code 5) provides details on the rationale and methods used to derive the carcinogenicity values found in IRIS. Users are referred to Section I for information on long-term toxic effects other than carcinogenicity.

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__II.A. EVIDENCE FOR CLASSIFICATION AS TO HUMAN CARCINOGENICITY

___II.A.1. WEIGHT-OF-EVIDENCE CLASSIFICATION

Classification -- D; not classifiable as to human carcinogenicity.

Basis -- Orally administered technical xylene mixtures did not result in significant increases in incidences in tumor responses in rats or mice of both sexes.

___II.A.2. HUMAN CARCINOGENICITY DATA

None.

<<< Xylenes >>>

___II.A.3. ANIMAL CARCINOGENICITY DATA

Inadequate. In an NTP (1986) study, 50 male and 50 female F344/N rats were treated by gavage with mixed xylenes in corn oil (60% m-xylene, 14% p-xylene, 9% o-xylene and 17% ethylbenzene) at dosages of 0, 250 or 500 mg/kg/day, 5 days/week for 103 weeks. Similarly, 50 male and 50 female B6C3F1 mice were treated with the same xylene mixture at dosages of 0, 500 or 1000 mg/kg/day. Animals were killed and examined histologically when moribund or after 104-105 weeks. An apparent dose-related increased mortality was observed in male rats, but this difference was statistically significant for the high dose group, only. No other differences in survival between dosage groups of either sex were observed. Interstitial cell tumors of the testes could not be attributed to administration of the test compound observed in male rats (43/50 control, 38/50 low-dose and 41/49 high-dose). NTP (1986) reported that there were no significant changes in the incidence of neoplastic or nonneoplastic lesions in either the rats or mice that could be considered related to the mixed xylene treatment, and concluded that under the conditions of these 2-year gavage studies, there was "no evidence of carcinogenicity" of xylene (mixed) for rats or mice of either sex at any dosage tested.

Maltoni et al. (1985), in a limited study, reported higher incidences (compared with controls) of malignant tumors in male and female Sprague-Dawley rats treated by gavage with xylene in olive oil at 500 mg/kg/day, 4 or 5 days/week for 104 weeks. This study did not report survival rates or specific tumor types; therefore, the results cannot be interpreted.

Berenblum (1941) reported that "undiluted" xylene applied at weekly intervals produced one tumor-bearing animal out of 40 after 25 weeks in skin-painting experiments in mice. No control groups were described. Pound (1970) reported negative results in initiation-promotion experiments with xylene as the initiator and croton oil as the promotor.

<<< Xylenes >>>

___II.A.4. SUPPORTING DATA FOR CARCINOGENICITY

The frequency of sister chromatid exchanges and chromosomal aberrations were nearly identical between a group of 17 paint industry workers exposed to xylene and their respective referents (Haglund et al., 1980). In vitro, xylene caused no increase in the number of sister chromatid exchanges in human lymphocytes (Gerner-Smidt and Friedrich, 1978). Studies indicate that xylene isomers, technical grade xylene or mixed xylene are not mutagenic in tests with Salmonella typhimurium (Florin et al., 1980; NTP, 1986; Bos et al., 1981) *nor in mutant reversion assays with Escherichia coli (McCarroll et al., 1981).* Technical grade xylene, but not o- and m-xylene, was weakly mutagenic in Drosophila recessive lethal tests. Chromosomal aberrations were not increased in bone marrow cells of rats exposed to xylenes by inhalation (Donner et al., 1980).

__II.B. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM ORAL EXPOSURE

Not available.

__II.C. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM INHALATION EXPOSURE

Not available.

__II.D. EPA DOCUMENTATION, REVIEW, AND CONTACTS (CARCINOGENICITY ASSESSMENT)
<<< Xylenes >>>

___II.D.1. EPA DOCUMENTATION

U.S. EPA. 1987. Drinking Water Criteria Document for Xylene. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Drinking Water, Washington, DC. ECAO-CIN-416. Final.

___II.D.2. REVIEW (CARCINOGENICITY ASSESSMENT)

The Drinking Water Criteria Document for Xylene has received Agency and external review.

Agency Work Group Review: 12/02/87

Verification Date: 12/02/87

___II.D.3. U.S. EPA CONTACTS (CARCINOGENICITY ASSESSMENT)

Larry Anderson / ODW -- (202)382-7587 / FTS 382-7587

W. Bruce Peirano / ORD -- (513)569-7540 / FTS 684-7540

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_III. HEALTH HAZARD ASSESSMENTS FOR VARIED EXPOSURE DURATIONS

Substance Name -- Xylenes
CASRN -- 1330-20-7

Not available at this time

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_IV. U.S. EPA REGULATORY ACTIONS

Substance Name -- Xylenes
CASRN -- 1330-20-7
Last Revised -- 03/01/88

EPA risk assessments may be updated as new data are published and as assessment methodologies evolve. Regulatory actions are frequently not updated at the same time. Compare the dates for the regulatory actions in this section with the verification dates for the risk assessments in sections I and II, as this may explain inconsistencies. Also note that some regulatory actions consider factors not related to health risk, such as technical or economic feasibility. Such considerations are indicated for each action. In addition, not all of the regulatory actions listed in this section involve enforceable federal standards. Please direct any questions you may have concerning these regulatory actions to the U.S. EPA contact listed for that particular action. Users are strongly urged to read the background information on each regulatory action in Background Document 4 in Service Code 5.

__IV.A. CLEAN AIR ACT (CAA)

No data available

------<<< Xylenes >>>------

__IV.B. SAFE DRINKING WATER ACT (SDWA)

___IV.B.1. MAXIMUM CONTAMINANT LEVEL GOAL (MCLG) for Drinking Water

Value (status) -- 0.44 mg/L (Proposed, 1985)

Considers technological or economic feasibility? -- NO

Discussion -- An MCLG of 0.44 mg/L for xylene is proposed based upon a DWEL of 2.2 mg/L and an assumed drinking water contribution of 20%. A DWEL (provisional) of 2.2 mg/L was calculated from a NOAEL of 337 mg/cu.m (only dose tested) for body weight, hematology and histopathologic effects in rats, guinea pigs, monkeys and dogs in a 90-day inhalation study (Jenkins, 1970). An uncertainty factor of 1000 was applied and human water consumption of 2 L/day was assumed.

Reference -- 50 FR 46936 Part IV (11/13/85)

EPA Contact -- Yogentra Patel / Criteria and Standards Division, ODW / (202)382-7571 / FTS 382-7571; or Drinking Water Hotline / (800)426-4791

------<<< Xylenes >>>------

__IV.C. CLEAN WATER ACT (CWA)

No data available

------<<< Xylenes >>>------

__IV.D. FEDERAL INSECTICIDE, FUNGICIDE, AND RODENTICIDE ACT (FIFRA)

No data available

------<<< Xylenes >>>------

__IV.E. TOXIC SUBSTANCES CONTROL ACT (TSCA)

No data available

------<<< Xylenes >>>------

__IV.F. RESOURCE CONSERVATION AND RECOVERY ACT (RCRA)

___IV.F.1. RCRA APPENDIX IX, for Ground Water Monitoring

Status -- Listed

Reference -- 52 FR 25942 (07/09/87)

EPA Contact -- Jerry Garman / OSW / (202)382-4658 / FTS 382-4658

------<<< Xylenes >>>------

__IV.G. SUPERFUND (CERCLA)

___IV.G.1. REPORTABLE QUANTITY (RQ) for Release into the Environment

Value (status) -- 1000 pounds (Final, 1985)

Considers technological or economic feasibility? -- NO

Discussion -- The final RQ is based on ignitability and aquatic toxicity as established for xylene under Section 311(b)(4) of the Clean Water Act (40 CFR 117.3). The available data indicate the aquatic 96-hour Median Threshold Limit for xylene is between 10 and 100 ppm, corresponding to an RQ of 1000 pounds. The ignitibility RQ of 1000 pounds is based on a flash point of 81 to 90F.

Reference -- 50 FR 13456 (04/04/85)

EPA Contact -- RCRA/Superfund Hotline

(800)424-9346 / (202)382-3000 / FTS 382-3000

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_V. SUPPLEMENTARY DATA

Substance Name -- Xylenes
CASRN -- 1330-20-7

Not available at this time

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_VI. BIBLIOGRAPHY

Substance Name -- Xylenes
CASRN -- 1330-20-7
Last Revised -- 07/01/89

__VI.A. ORAL RfD REFERENCES

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------<<< Xylenes >>>------

__VI.B. INHALATION RfD REFERENCES

None

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__VI.C. CARCINOGENICITY ASSESSMENT REFERENCES

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__VI.D. DRINKING WATER HA REFERENCES

None

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SYNONYMS

108-38-3
1330-20-7
2106-42-3
95-47-6
dimethylbenzene
1,2-dimethylbenzene
1,3-dimethylbenzene
1,4-dimethylbenzene
mixed xylenes
m-xylene
meta-xylene
o-xylene
ortho-xylene
p-xylene
para-xylene
Xylenes